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Orbitofrontal sulcogyral morphology: its distribution, structural and functional associations, and predictive value in different diagnostic groups

The theory of predictive associations of the orbitofrontal sulcogyral patterns

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ABSTRACT OF THESIS

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Bipolar affective disorder and schizophrenia are highly heritable psychiatric illnesses and the leading causes of worldwide disability. The orbitofrontal cortex (OFC) is a region of the frontal lobe with wide spread connectivity with other brain areas involved in reward, motivation and emotion. Evidence from various neuroimaging, genetic, post-mortem and brain lesion studies suggest

that orbitofrontal cortex may play a role in pathophysiology of mental illnesses.

This thesis sought to investigate the pathogenesis of major psychiatric illnesses through the investigation of orbitofrontal morphology in schizophrenia and bipolar disorder and through its associations with brain structure and function. Orbitofrontal morphology and its structural and functional associations were examined in healthy controls, patients with schizophrenia or bipolar affective disorder, and those at high genetic risk using functional and structural MRI.

In the first study we found that the orbitofrontal type III is more frequent and the orbitofrontal type I is less common in the right hemisphere in patients with schizophrenia while in patients with bipolar disorder type III appears more often in both left and right hemispheres. We then sought to examine the relationship of orbitofrontal morphology to disease risk in a study of 146 people at high risk of developing schizophrenia and 110 people at high risk of developing bipolar disorder. We discovered that in the unaffected high risk groups the orbitofrontal type III predicted the development of later psychiatric illnesses, when combined with anterior cingulate morphology. Finally we showed, in a further study, that OFC morphology was associated with measures of schizotypy, brain structure, brain function and cognition.

In conclusion, orbitofrontal morphology is linked to major psychiatric disorder and has significant structural and functional associations. As orbitofrontal sulcogyral patterns are formed in early life a fuller awareness of their relevance to brain function holds out the prospect that we could use such measures as an indicator of vulnerability to the development of illness later in life. This work points to the potential for the foundation of a theory of predictive associations between morphological patterns and the development of psychosis.

Content

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My most special thanks go to Dr. T. William J. Moorhead and to Dr. Heather C. Whalley for their friendship, support and guidance during all years of my PhD. Dr. Moorhead introduced me into the area of structural MRI. Through him I fell in love with science. He always encouraged me to believe in my own intuition and to develop my own ideas. Both Dr. Moorhead and to Dr. Heather Whalley helped me enormously by teaching me the way to design my experiments, to process and analyze functional Magnetic Resonance

Images and to run morphometric analyses. I am very grateful to both of them for being there for me when I needed their help.

I am also grateful to Dr. Andrew C. Stanfield and to Dr. Killian A. Welch for helping to develop the identification protocol of the orbitofrontal sulcogyral patterns. I would like to express my gratitude to Dr. Mahsa Shokouhi (the University of Glasgow) for her advice on the application of the BrainVISA software. My sincere gratitude goes to Dr. S.M. Meredith and Dr. N.C.A. Whyler for rating the anterior cingulate morphology in the EHRS and to Dr. C. Carstairs, who assisted me in the rating of the paracingulate sulcus in the Bipolar Family Study and in the Psychosis Study.

I will be always grateful to my colleagues (Dr. Jessica E.D. Sussmann, Dr. Emma Sprooten, Dr. Liana Romaniuk, Martina Papmeyer, Maria Regina Dauvermann, Dr. Prerona Mukherjee, and Dr. Stephen Giles) for their support and friendship. I am especially thankful to Dr. Prerona Mukherjee and Maria Regina Dauvermann for their help in implementing functional and effective connectivity analyses.

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Finally, I would like to thank my family, especially my son and husband for supporting me during my studies. Their continuing love and support are priceless.

Declaration

I, Goultchira Chakirova, declare that:

1. This thesis was composed by myself;
2. The work contained in this thesis is my own;
3. The work has not been submitted for any other degree or professional qualification except as specified;
4. The work was completed whilst I was doing PhD at the University of Edinburgh, Division of Psychiatry.

Signed:

(Goultchira Chakirova)

Overview of the thesis

The aim of this project was to assess the orbitofrontal morphology considering its distribution, structural and functional associations, its associations with the anterior cingulate morphology in various diagnostic groups and its predictive value in those at high risk of developing schizophrenia and bipolar affective disorder. This work was conducted in three cohorts made available by the Division of Psychiatry: the Psychosis Study, the Edinburgh High Risk Study and the Bipolar Family Study. This was a unique opportunity to examine and to compare the orbitofrontal sulcogyral patterns in a relatively large number of brain images. The value of these morphological measures was examined by assessing vulnerability to schizophrenia and bipolar affective disorder. This work adds to the research on orbitofrontal sulcogyral patterning conducted by the Harvard Medical School (Boston, USA), Yokohama City University, School of Medicine (Yokohama, Japan) and the University of Florida (USA).

This thesis consists of eight chapters. **Chapter 1** is concerned with the human orbitofrontal cortex, its localization, architectonic structure, sulcogyral morphology, neurochemical modulation, neurophysiology, function and connections with the other brain regions. Frontal lobe lesions studies are reviewed and neuropsychological assessments designed to investigate the orbitofrontal cortex are described.

Chapter 2 reviews the literature concerning the aetiology and pathogenesis of schizophrenia and bipolar disorder. This chapter contains a summary of the structural and functional neuroimaging findings related to the orbitofrontal cortex in patients with schizophrenia and bipolar disorder and in those at high genetic risk of developing illness. Connectivity findings associated with

schizophrenia and bipolar disorder are discussed as these may provide a reasonable explanation of the structural and functional MRI findings.

Chapter 3 considers the distribution of the orbitofrontal sulcogyral patterns and anterior cingulate morphology, the associations of the orbitofrontal sulcogyral patterns with neuropsychological measures as well as the associations between the orbitofrontal patterns and paracingulate sulcus. These associations were examined in patients with schizophrenia, patients with bipolar disorder and their unaffected relatives in the Psychosis Study. The BrainVISA software which provided the automated sulci recognition was considered as the basis for a semi-automated method for recognition of orbitofrontal sulcogyral patterns. Dr. C. Carstairs assisted in rating of the paracingulate sulcus in the Psychosis Study. The second rater for the orbitofrontal morphology was Dr. Killian A. Welch, who, along with Dr. Andrew C. Stanfield also assisted in the development of the manual identification protocol of the orbitofrontal sulcogyral patterns. Dr. Mahsa Shokouhi (the University of Glasgow) advised on the application of the BrainVISA software.

Chapter 4 describes orbitofrontal morphology and its association with the paracingulate sulcus, brain volume and neuropsychological scores in the Edinburgh High Risk Study. The symmetry/asymmetry scores and the gender effect on the orbitofrontal and anterior cingulate morphology were reported. Positive and negative predictive values were evaluated as well as the sensitivity of orbitofrontal morphology in discriminating between high risk subjects who remain well and those similarly at risk who become ill. These tests show that the orbitofrontal patterns in combination with the anterior cingulate morphology provide an indication of increased vulnerability to the development of schizophrenia. The identification of the cingulate and paracingulate morphological variants was initially performed by Dr. S.M. Meredith and Dr. N.C.A. Whyler and these assessments were continued by

Dr. G. Chakirova and Dr. C. Castairs. Dr. Killian A. Welch assisted on rating the orbitofrontal morphology. Results from this chapter were published in Chakirova *et al.* (2010) and in Meredith *et al.* (2012).

In **Chapter 5** the following was analysed: the distribution of the orbitofrontal sulcogyral patterns and its associations with the paracingulate sulcus, brain volume and neuropsychological scores in the Bipolar Family Study. This analysis followed the analysis protocol applied to the Edinburgh High Risk Study in **Chapter 4**. The results covered the symmetry/asymmetry scores for the orbitofrontal and anterior cingulate morphology, and a gender effect on the orbitofrontal and cingulate morphology. Positive and negative predictive values and sensitivity were calculated. Dr. C. Carstairs assisted in rating of the paracingulate and cingulate sulci in the Bipolar Family Study.

Chapter 6 describes differences in brain structure which were found to be associated with orbitofrontal sulcogyral patterns in healthy individuals in the Bipolar Family Study. A grey matter density analysis was implemented using Voxel - Based Morphometry. Prof. David C. Glahn and Dr. Anderson M. Winkler (Yale University, New Haven, USA) extracted cortical thickness using the FreeSurfer software. Dr. T. William J. Moorhead advised on the tissue density and cortical thickness analyses. Healthy individuals with the orbitofrontal type III had reduced grey matter density and reduced cortical thickness in the frontal region compared to those with the orbitofrontal type I.

Chapter 7 reported the brain activation differences that were found in healthy volunteers and the association of these differences with orbitofrontal patterns. This analysis was performed under supervision of Dr. Heather Whalley.

Chapter 8 summarized the research findings and considered how the development of morphological pattern measures could assist in the clinical

diagnosis of psychosis. There were important associations found between the presentation of orbitofrontal patterns and the paracingulate sulcus in those at high risk of developing illness. This work points to the potential for the foundation of a theory of predictive associations between morphological patterns and the development of psychosis.

The PPI (Psycho-Physiological Interactions) analysis (Appendix IV) was performed under supervision of Dr. Prerona Mukherjee who also wrote a script to run PPI in Matlab.

List of publications:

Peer-reviewed articles:

1. **Chakirova, G.**, Welch, K.A., Moorhead, T.W.J., Stanfield, A.C., Hall, J., Skehel, P., Brown, V.J., Johnstone, E.C., Owens, D.G.C., Lawrie, S.M., McIntosh, A.M. 2010. Orbitofrontal morphology in people at high risk of developing schizophrenia. *European Psychiatry* 25 (6): 366 - 372.

2. **Chakirova, G.**, Whalley, H.C., Thomson, P.A., Hennah, W., Moorhead, T.W.J., Welch, K.A., Giles, S., Hall, J., Johnstone, E.C., Lawrie, S.M., Porteous, D.J., Brown, V.J., McIntosh, A.M. 2011. The effects of DISC1 risk variants on brain activation in controls, patients with bipolar disorder and patients with schizophrenia. *Psychiatry Research: Neuroimaging* 192: 20 – 28.

3. Whalley, H.C., Sussmann, J., **Chakirova, G.**, Mukerjee, P., Peel, A., McKirdy, J., Hall, J., Johnstone, E.C., Lawrie, S.M., McIntosh, A.M. 2011. The neural basis of familial risk and temperamental variation in individuals at high risk of bipolar disorder. *Biological Psychiatry* 70 (4): 343 - 349.

4. Whalley, H.C., Sussmann, J.E., Johnstone, M., Romaniuk, L., Redpath, H., **Chakirova, G.**, Mukherjee, P., Hall, J., Johnstone, E.C., Lawrie, S.M., McIntosh, A.M. 2012. Effects of a mis-sense DISC1 variant on brain activation in two cohorts at high risk of bipolar disorder or schizophrenia. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics* 159B (3): 343 - 353.

5. Meredith, S.M., Whyler, N.C.A., Stanfield, A., **Chakirova, G.**, Moorhead, T.W.J., Job, D. E., Giles, S., McIntosh, A.M., Johnstone, E.C., Lawrie, S.M. 2012. Anterior cingulate morphology in people at genetic high-risk of schizophrenia. *European Psychiatry* 27 (5): 377 - 385.

6. Wardlaw, J.M., Brindle, W., Casado, A.M., Shuler, K., Henderson, M., Thomas, B., Macfarlane, J., Muñoz Maniega, S., Lymer, K., Morris, Z., Pernet, C., Nailon, B., Ahearn, T., Mumuni, A.N., Mugruza, C., McLean, J., **Chakirova, G.**, Tao, Y., Simpson, J., Stansfield, A., Johnston, H., Parikh, J., Royle, N.A., De Wilde, J., Bastin, M.E., Weir, N., Farrall, A., Valdes Hernandez, M.C. A systematic review of the utility of 1.5 versus 3 Tesla magnetic resonance brain imaging in clinical practice and research. *European Radiology* 22: 2295 - 2303.

7. **Chakirova, G.**, Sussmann, J.E.D., Hampshire, A., Moorhead, T.W.J., Welch, K.A., Peel, A., Mukherjee, P., Whalley, H.C., Owen, A.M., Hall, J., Johnstone, E.C., Lawrie, S.M., McIntosh, A.M., Brown, V.J. Impairment in cognitive flexibility in patients with bipolar disorder versus patients with schizophrenia: is there any difference? The manuscript is prepared for submission.

8. Carstairs, C., **Chakirova, G.**, Sussmann, J.E., Glahn, D., Winkler, A., Whalley, H.C., Moorhead, T.W.J., Giles, S., Lawrie, S.M., McIntosh, A.M. Anterior cingulate morphology in those at high genetic risk of developing bipolar disorder. The manuscript is in preparation.

Published abstracts:

9. **Chakirova, G**., Sussmann, J.E., Hampshire, A., Moorhead, T.W.J., Welch, K.A., Peel, A., Mukherjee, P., Whalley, H.C., Owen, A.M., Hall,

J., Johnstone, E.C., Lawrie, S.M., McIntosh, A.M., Brown, V.J. 2012. Impairment in cognitive flexibility in patients with bipolar disorder versus patients with schizophrenia *Schizophrenia Research* 136 (1): S143.

10. **Chakirova, G**., Moorhead, T.W.J., Whalley, H.C, Sussmann, J.E., Glahn, D., Winkler, A., Welch, K.A., Giles, S., Stanfield, A.C., Brown, V.J., Hall, J., Johnstone, E.C., Lawrie, S.M., McIntosh, A.M. 2012. Grey matter density and cortical thickness vary with different orbitofrontal sulcogyral patterns. *Schizophrenia Research* 136 (1): S202.

11. **Chakirova, G**., Welch, K., Moorhead, T.W.J., Stanfield, A.C., Hall, J., Lawrie, S.M., Johnstone, E.C., Brown, V.J., McIntosh, A.M. 2009. Comparison of alteration of orbitofrontal sulcogyral pattern in people with bipolar disorder and their unaffected relatives: is there any difference? *Abstract Supplement to Journal of Psychopharmacology*, 23 (6): p. A50.

12. **Chakirova, G**., Welsh, K.A., Moorhead, T.W.J., Stanfield, A.C., Hall, J., Lawrie, S.M., Johnstone, E.C., Brown, V.J., McIntosh, A.M. 2009. 'Investigation of orbitofrontal sulcogyral pattern: is it possible to distinguish individuals with schizophrenia from those with bipolar disorder?' *The World Journal of Biological Psychiatry* 10 (1): p145.

13. **Chakirova, G**., Thomson, P., Whalley, H.C., Hennah, W., Hall, J., Johnstone, E.C., Lawrie, S.M., McIntosh, A.M. 2009. 'Risk variants of DISC1 exhibit different activations during the Hayling Sentence Completion Task in bipolar disorder and schizophrenia.' *Brit. Neurosci. Assoc. Abstr.,* vol 20, p. 137. 20th National Meeting of the British Neuroscience Association 2009.

14. **Chakirova, G**., Moorhead, T.W.J., Stanfield, A.C., Harris, J.M., Sprooten, E., Philip, R., Mukherjee, P., Romaniuk, L., Cunningham Owens, D.G., Hall, J., Lawrie, S.M., Johnstone, E.C., McIntosh, A.M. 2008. Orbitofrontal sulcogyral patterns in people at high-risk of developing schizophrenia. *FENS Forum Abstracts*, p342. 6th FENS Forum of European Neuroscience, 2008.

15. **Chakirova, G**., Erohina, E.A., Bazhutina, T.O. 2000. Investigation of the effect of the unconsciousness on the regression of pathological processes. *Materials of the Novosibirsk Interuniversity Scientific Conference 'Intellectual potential of Siberia',* p. 118 - 120. Published in Russian.

16. **Chakirova, G**. 2000. The research of the structure of the human psyche using trance conditions. *Materials of the 60-th and 61-st Final Scientific Conference of the students and young scientists,* p. 271. Published in Russian.

17. **Chakirova, G**., Erohina, E.A. 1999. Investigation of the unconsciousness: the separable reality of Carlos Castaneda. *Materials XXXVII of the International Scientific Conference 'The student and scientific and technical progress',* p. 142 - 143. Published in Russian.

The purpose of the present study

The purpose of the present study was to examine associations between the orbitofrontal sulcogyral patterns and different characteristics of patients with schizophrenia or bipolar disorder. Moreover, it was important to investigate whether orbitofrontal patterns on their own or in combination with the other structural patterns would predict the development of schizophrenia or bipolar disorder in a high risk population. The hypotheses were that:

1. orbitofrontal patterns in combination with anterior cingulate morphology will predict development of schizophrenia or bipolar affective disorder;
2. different orbitofrontal patterns will represent structural and functional alterations even within healthy population;
3. there will be neuropsychological findings associated with orbitofrontal patterns in a high risk population.

In order to test the hypotheses the orbitofrontal patterns were rated and examined in three different cohorts: the Edinburgh High Risk Study (See **Chapter 4** for details), the Bipolar Family Study (See **Chapter 5**, **6** and **7** for details) and the Psychosis Study (See **Chapter 3** for details) which included adult patients with bipolar disorder and schizophrenia, and their unaffected relatives. Structural and functional magnetic resonance imaging scans were used with the application of the sulcal pattern classification protocol and Voxel-Based Morphometry analysis. Psycho-Physiological Interactions (PPIs) were also examined.

Chapter 1

The Orbitofrontal cortex

This chapter is concerned with the human orbitofrontal cortex, its localization, architectonic structure, sulcogyral morphology, neurochemical modulation, neurophysiology, function and connections with the other brain regions. Frontal lobe lesions studies are reviewed and neuropsychological assessments designed to investigate the orbitofrontal cortex are described.

1.1 Introduction

The frontal lobe was previously found to be associated with a number of cognitive functions including executive functioning. Given that executive functions were found impaired in schizophrenia and bipolar disorder, the frontal lobe was of particular interest in research studies. ***The purpose of such studies was to identify markers that might help to increase the accuracy of prediction of schizophrenia and bipolar disorder in genetically high-risk families.*** The orbitofrontal cortex (OFC) is a large region of the frontal lobe. Its importance is based upon the part it plays in multiple cognitive functions and its wide spread connectivity with the other brain areas. In the present study the orbitofrontal cortex was examined as a brain region where the structural abnormalities indicating potential mental health problems could be identified. This is based upon the functionality of the orbitofrontal cortex, its connections with the other brain areas, its influence on the cerebral cortex, its genetic associations and structural characteristics. What follows is a summary of research addressing the structure and function of the OFC and its connectivity, as well as a discussion of the work of Chiavaras (Chiavaras and Petrides, 2000), Nakamura (Nakamura *et al.,* 2007) and Chakirova and colleagues (2010). The contributed studies include neuroimaging, genetic, post-mortem and lesion case research.

1.1.1 Frontal lobe lesion case studies

Sources of damage to the orbitofrontal region include closed head injuries, penetrating head wounds, cerebrovascular accidents, neurosurgical excisions and neurodegenerative disorders. Damage to the orbitofrontal cortex due to closed head injuries and penetrating head wounds occurs relatively often. However, the trauma of the OFC in those cases is rarely specific and isolated as many other brain regions would be often also injured.

The most widely described case of frontal lobe injury is that of Phineas Gage (see in details in **1.1.1.1**).

The cerebrovascular accidents are also very common source of the OFC injury due to ruptured aneurysms. The vascular supply of the orbitofrontal cortex is described in details in **1.2.3.**

A number of neurodegenerative disorders can cause an impairment of the orbitofrontal functions. However, in these cases a dysfunction of the orbitofrontal function is a part of the larger neuropathological process. For the frontal variant of frontotemporal dementia the OFC would be a primary region for the pathological manifestation this illness (Broe *et al.,* 2003; Varrone *et al.,* 2004; Franceshsi *et al.,* 2005; Williams *et al.,* 2005).

1.1.1.1 Phineas Gage

There is a well-known example of the changes associated with severe frontal lobe damage. A man named Phineas Gage, who was a railroad worker in New England, was injured in accident explosion in 1848. A large tamping rod went through the left side of Gage's jaw and came out at the top of his skull. He survived the brain injury that primarily affected the left frontal lobe from the medial orbitofrontal area upward to the precentral cortex. In the weeks following the accident Phineas Gage was in coma and suffered meningitis. After recovery he returned to his railroad job. However, he was fired because his intellect, personality and emotional stability had remarkably changed. Phineas became impulsive and started acting in a childlike manner. He lost his ability to adapt to the social environment. His friends and acquaintances said that Gage was no longer Gage they knew.

Gage travelled widely and he had many different jobs. In 1852 he went to work for a coach line to drive horses in Chile. After spending several years in

South America he came back to California where he died. This case was the first to highlight the importance of the frontal lobe in the representation of personality and in executive function.

1.1.1.2 A single case study

In 1996 Pang and Lewis recorded the case of an orbitofrontal cortex lesion which they observed for a period over 6 years. Prior to the accident which caused the OFC lesion the patient had shown symptoms of bipolar affective disorder. Moreover, some of his first degree relatives were also affected with bipolar disorder and were not diagnosed with any other mental illnesses. By the time of the accident the patient had had three episodes of mood disturbance without psychosis. During his third episode the patient survived severe damage to the left prefrontal cortex and partially to the left temporal region. Nine months after the trauma he developed treatment - resistant schizophrenia having such symptoms as delusions, hallucinations, formal thought disorder and social withdrawal but showing no signs of mood disturbance. So, damage to the left prefrontal cortex in this patient appeared to change his bipolar disorder into schizophrenia. This case suggests that orbitofrontal cortex as a part of the frontal lobe is associated with schizophrenia and bipolar affective disorder and will be further discussed in **Chapter 8**.

1.1.1.3 Other brain lesion studies

The case studies, described above, suggest that the orbitofrontal cortex may play a role in the neuropathophysiology of mental illnesses. At least some clinical features of schizophrenia and bipolar disorder could be related to structural and functional abnormalities of orbitofrontal cortex. Animals studies report that lesion of the orbitofrontal cortex may lead to a more aggressive behaviour, to an increase in social withdrawal, and alterations in appetite

(Fuster, 1989; Raleigh and Steklis, 1981). Furthermore, the human lesion studies associated orbitofrontal morphology with behavioural abnormalities, including depressed mood, anger, irritability, affective instability, and anxiety symptoms (Grafman *et al.,* 1986, 1996). Moreover, other studies reported association of the orbitofrontal cortex damage with not only impairment in emotional and social behaviour but also with decision-making (Damasio *et al.,* 1990; Rolls *et al.,* 1994; Blair, 1995; Hornak *et al.,* 1996; Stone *et al.,* 1998; Blair and Cipolotti, 2000; Beer *et al.,* 2003; Hornak *et al.,* 2003; Beer *et al.,* 2006; Bramham *et al.,* 2009) as well as with explicit facial expression deficit (Hornak *et al.,* 1996; Heberlein *et al.,* 2008). Furthermore, a number of lesion and imaging studies reported that dysfunction of the orbitofrontal cortex was found to be associated with frequently observed clinical features of bipolar affective disorder, including impairment in reward-based decision making, impulsivity and substance abuse (London *et al.,* 2000; Bechara, 2004; Kringelbach, 2005). These reports imply an involvement of the orbitofrontal morphology in the pathophysiology of various mental illnesses, including schizophrenia and bipolar disorder.

The purpose of the present study was to examine associations between the orbitofrontal sulcogyral patterns and different characteristics of patients with schizophrenia or bipolar disorder. Moreover, it was important to investigate whether orbitofrontal patterns on their own or in combination with the other structural patterns would predict the development of schizophrenia or bipolar disorder in a high risk population. The hypotheses were as follows:

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1.2 Anatomy, neurophysiology and function of the orbitofrontal cortex

The orbitofrontal cortex is a large and multifunctional region that lies in the anterior cranial fossa and forms the ventral surface of the frontal lobe (See **Figure 1.1**). The morphological borders of the orbitofrontal surface are the ventromedial margin of the cerebral hemisphere, the ventrolateral prefrontal cortex, the anterior perforated substance caudally and the frontal pole rostrally.

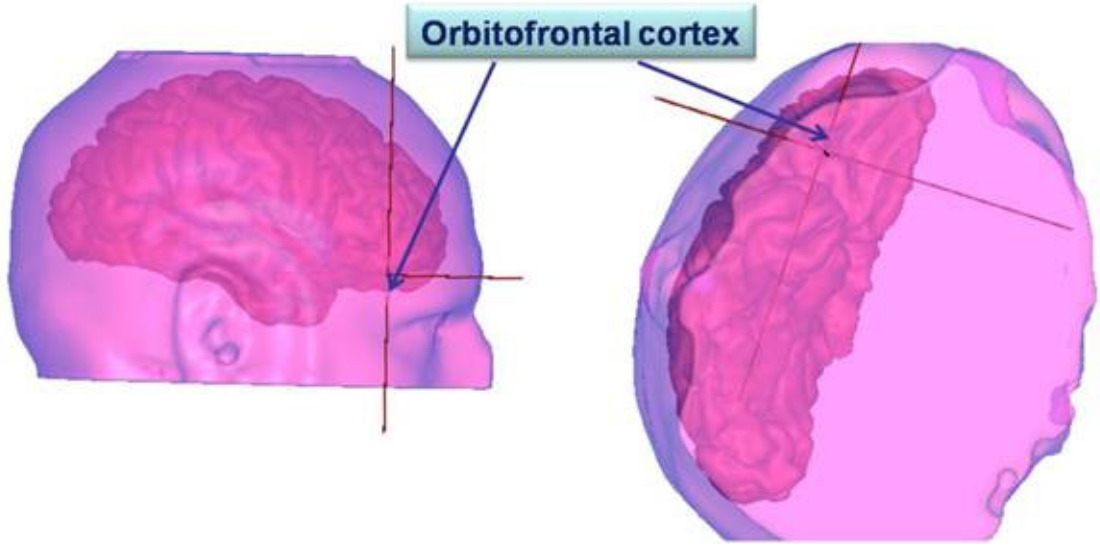


Figure 1.1. Localization of the orbitofrontal cortex. This image was created using the BrainVisa software (http://www.brainvisa.info).

1.2.1 Architectonic structure of the orbitofrontal cortex

Cytoarchitectonic analyses of the cortex have revealed that it contains neuronal cell bodies and intracortical axon tracts which can be grouped into

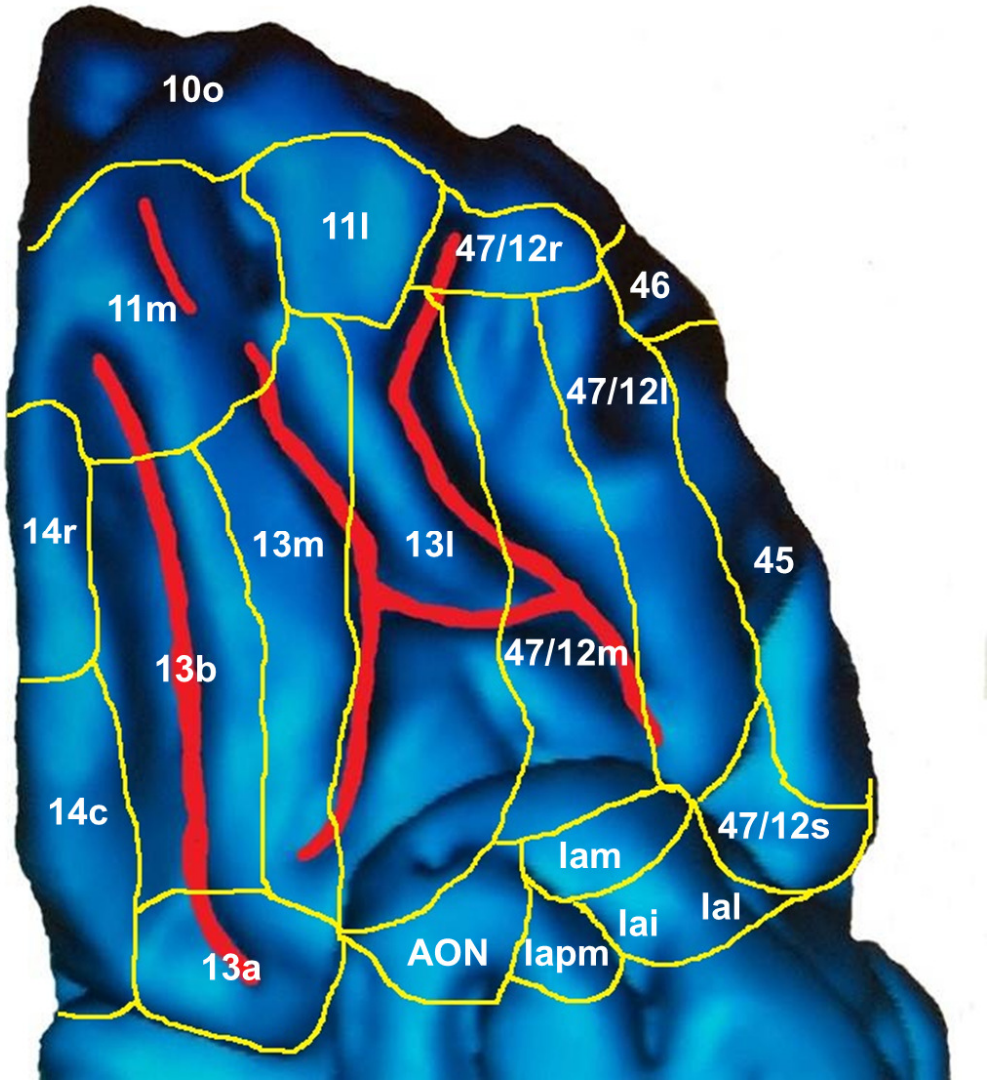
six main layers directing from outside or pial surface to inside or white matter. These layers are the molecular layer I, the external granular layer II, the external pyramidal layer III, the internal granular layer IV, the internal pyramidal layer V and the multiform layer VI. The neurons of the cerebral cortex can be subdivided into two main groups: excitatory (80% of neurons, represented by pyramidal neurons) and inhibitory (being in a minority – 20%). The inhibitory neurons are known as local circuit neurons since their axons are 'intrinsic' (do not enter white matter). This group is formed by various brain cells including basket cells and chandelier cells (Shipp, 2007).

All six layers vary from each other by the type and size of neurons sited in the particular layer. The extensions of apical dendritic tufts of pyramidal neurons, horizontally-oriented axons and glial cells can be mainly identified in the molecular layer I (Shipp, 2007). However, Cajal - Retzius cells and spiny stellate neurons can be found here as well. This layer receives input from the cells of thalamus (Rubio - Garrido *et al.,* 2009) which is thought to be important for the 'feedback' interactions in the cerebral cortex particularly in such brain functioning as associative learning and attention (Gilbert and Sigman, 2007). The external granular layer II consists of small pyramidal neurons and stellate neurons. In the external layer III pyramidal neurons are predominantly small and medium - sized. This layer also contains non - pyramidal neurons with vertically - oriented axons. Layers I, II and III provide with interhemispheric corticocortical afferent (conveying towards a centre) connections. Additionally, layer III is the main supply of corticocortical efferent (conveying away from a centre) connections. In the internal layer IV different types of stellate and pyramidal neurons could be identified. This area is connected with thalamus and the other cortical regions through thalamocortical and intra-hemispheric corticocortical afferents (Jones, 1998). There are some cortical areas which contain only a rudimentary layer IV (dysgranular) or no layer IV at all (agranular) (Dombrowski *et al.,* 2001).

The large pyramidal neurons including the Betz cells (pyramidal neurons in the primary motor cortex, named after scientist Vladimir Betz) are mainly represented in the internal pyramidal layer V. This layer is known as a source of subcortical efferents. Layer VI, which forwards efferent excitatory and inhibitory fibres to the thalamus, establishes reciprocal interconnection between the thalamus and the cortex, and contains multiform neurons, small spindle-like pyramidal neurons and few large pyramidal neurons (Creutzfeldt, 1995). All six layers and different neuronal types are connected between each other (Mountcastle, 1997; Hubel and Wiesel, 1959) and their connections are grouped into cortical columns and minicolumns (or the basic functional units of cortex).

Based on subtle variations in the laminar structure the orbitofrontal cortex was subdivided into five major subregions (known as Brodmann' areas; See **Figure 1.2**), including frontal polar area 10, area 11 anterior, area 13 caudal, area 14 medial, and area 12 lateral (Walker, 1940; Barbas and Pandya, 1989; Carmichael and Price, 1994; Petrides and Pandya, 1994). The lateral area 12 in monkeys is correspondent to area 47 in Brodmann's human map. This is why Michael Petrides suggested labelling this ventrolateral cortex as 47/12 instead of just area 12 to reconcile existed inconsistencies between Walker's monkey and Brodmann's human cytoarchitectonic maps (Petrides and Pandya, 1994).

Figure 1.2. A schematic human cytoarchitectonic map of the orbitofrontal cortex. AON = anterior olfactory nucleus.



Recent findings of Von Economo neurons in layer V of frontoinsular area and the anterior cingulate cortex suggest involvement of these large bipolar neurons in a number of cognitive functions including decision-making, awareness and error recognition (Watson *et al.,* 2006; Allman *et al.,* 2010).

Strikingly, these neurons were discovered mostly in humans and in much less representation in great apes. Moreover, Von Economo neurons were significantly prevalent in the right hemisphere where the orbitofrontal patterns were found altered in patients with schizophrenia (Nakamura *et al.,* 2007) and in those at high risk of developing schizophrenia (Chakirova *et al.,* 2010). Given that Von Economo neurons appear in the 36th week of post-conception, around the same time as the orbital sulci and the paracingulate sulcus form it may suggest that the dysfunction of Von Economo cells play a role in the neurodevelopment of schizophrenia and could be reflected in the formation of the orbitofrontal and paracingulate morphological variants. The latest evidence suggests that Von Economo neurons might be involved in autonomic regulation as well as in conditions that are characterised by impairment in emotional function and social skills (Butti *et al.,* 2013).

The orbitofrontal cortex could be subdivided into three areas depending on the number of layers in it. While the anterior part of the orbitofrontal cortex (isocortex) consists of 6 layers (granular orbitofrontal cortex), the posterior agranular non-isocortical part of the OFC consists of only three layers (Morecraft *et al.,* 1992). In between those areas gradual differentiation forms a dysgranular five to six layered cortex. This part of the OFC is characterized by poorly differentiated layer II, lack of sublimination in layers III and V, and poor demarcation of layer VI (Morecraft *et al.,* 1992).

Furthermore, evidence from the cytoarchitectonic and embryological studies may suggest a regional functional specialization of the orbitofrontal cortex. From the cytoarchitectonic point of view, the medial part of the OFC is more agranular, whereas the lateral area of the orbitofrontal cortex is more granular (Morecraft *et al.,* 1992; Carmichael and Price, 1994; Lacerda *et al.,* 2004). From the embryologic point of view, the lateral part of the orbitofrontal cortex develops from a paleocortical moiety, while the medial region of the OFC derives from an archicortical moiety (Zald and Kim, 2001).

1.2.2 Localization of the orbitofrontal cortex and Brodmann' areas

A straight gyrus, the gyrus rectus, is separated by the olfactory sulcus at the medial edge from the orbital surface. The cortex of the gyrus rectus is subdivided between Brodmann' areas (BA) 14 and 25. Two consecutively running sulci, laterally to the olfactory sulcus, could be identified as the medial orbital sulcus (MOS) and the lateral orbital sulcus (LOS). The lateral and medial orbital sulci are joined by the transverse orbital sulcus (TOS). The branches of the medial and lateral orbital sulci that lie anterior to the transverse orbital sulcus are named rostral parts of the MOS and LOS, while the branches of the medial and lateral orbital sulci that lie posterior to the TOS are called the caudal parts of the MOS and LOS. The area between the TOS and the rostral parts of the MOS and LOS is named the anterior orbital gyrus. This gyrus is occupied by Brodmann' area 11. The gyrus between the TOS and the caudal parts of the medial and lateral orbital sulci is occupied by BA 13.

1.2.3 The vascular supply of the orbitofrontal cortex

The orbital branches of the anterior cerebral artery provide the gyrus rectus and medial orbital gyrus with blood supply. The frontopolar branch of the anterior cerebral artery supplies the anterior orbitofrontal area. The orbital branch of the middle cerebral artery provides the lateral regions of the orbitofrontal cortex. Finally, the anterior communicating artery supplies the posterior aspects of the orbitofrontal cortex. The cerebrovascular accidents are very common source of the OFC injury due to ruptured aneurysms.

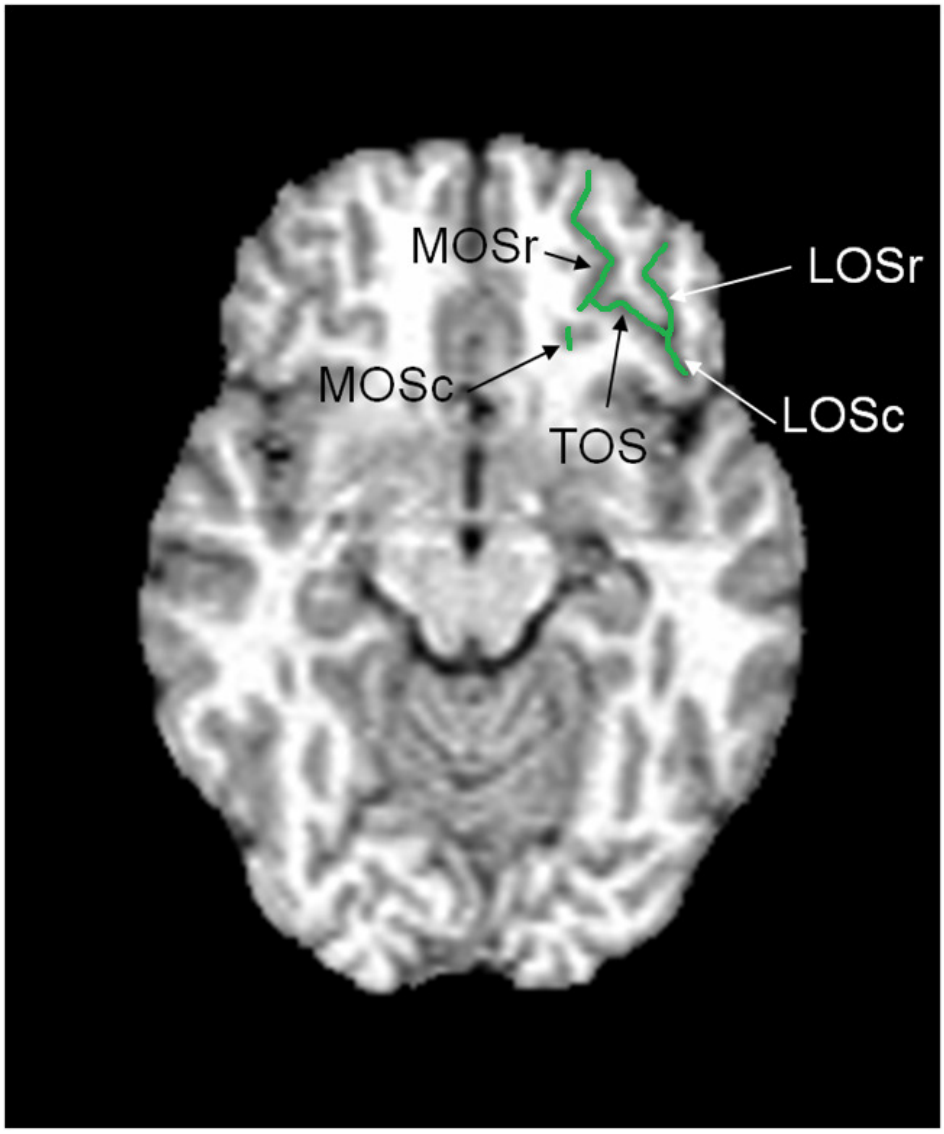
1.2.4 Sulcal and gyral morphology of the orbitofrontal cortex

1.2.4.1 Main orbitofrontal sulci and gyri (See Figure 1.3)

There are three orbital sulci that were previously described by Chiavaras and Petrides (2000) as well as by Nakamura and colleagues (2007). These are distinguishable in the orbitofrontal surface as the lateral orbital sulcus, medial orbital sulcus and transverse orbital sulcus. These are known as the main orbital sulci. They vary in length and connectivity and are located laterally to the olfactory sulcus. The medial, lateral and transverse orbital sulci were called the main orbital sulci as they are always present in the orbitofrontal cortex.

Based on the main orbital sulci (Duvernoy, 1991; Chiavaras and Petrides, 2000) the orbitofrontal area could be subdivided into the five following regions including the gyrus rectus (medial to the olfactory sulcus), the lateral orbital gyrus (lateral to the lateral orbital sulcus), the medial orbital gyrus (between the olfactory sulcus and the medial orbital sulcus), the anterior orbital gyrus (between the rostral parts of the lateral and medial orbital sulci and the transverse orbital sulcus) and the posterior orbital gyrus (between the caudal parts of the medial and lateral orbital sulci). Nakamura and colleagues (2008) united the medial, anterior and posterior orbital gyri into middle orbital gyrus based on his observation of the reduced variability of the olfactory and lateral orbital sulci.

Figure 1.3. The main orbital sulci in the left hemisphere coloured in green. LOSr = Lateral Orbital Sulci, part rostral; LOSc = Lateral Orbital Sulci, part caudal; MOSr = Medial Orbital Sulci, part rostral; MOSc = Medial Orbital Sulci, part caudal; TOS = Transverse Orbital Sulci.



1.2.4.2 Other orbitofrontal sulci

The appearance of additional sulci (the intermediate orbital sulcus, the posterior orbital sulci, and the sulcus fragmentosus) increases the variability and complexity of the orbitofrontal sulcogyral structure. There can be one or two intermediate orbital sulci (medial and lateral) that are localised between the rostral parts of the MOS and LOS and are anterior to the transverse orbital sulcus. The posterior orbital sulcus can be one or two (medial and lateral) and might be identified between the caudal parts of the medial and lateral orbital sulci and the transverse orbital sulcus. The sulcus fragmentosus is found between the medial orbital sulcus and the olfactory sulcus as one or two parts of the small sulcus. The intermediate orbital sulcus, the posterior orbital sulci, and the sulcus fragmentosus are called the additional sulci as they may not be present in the orbitofrontal cortex (Chiavaras and Petrides, 2000).

1.2.4.3 Orbitofrontal sulcal patterns

Orbitofrontal sulcogyral patterns were firstly classified by Chiavaras and Petrides (2000). Later this classification was expanded by adding a new type that was named type IV (Chakirova *et al.,* 2010).

1.2.4.3.1 Classification of Chiavaras (See Figure 1.4)

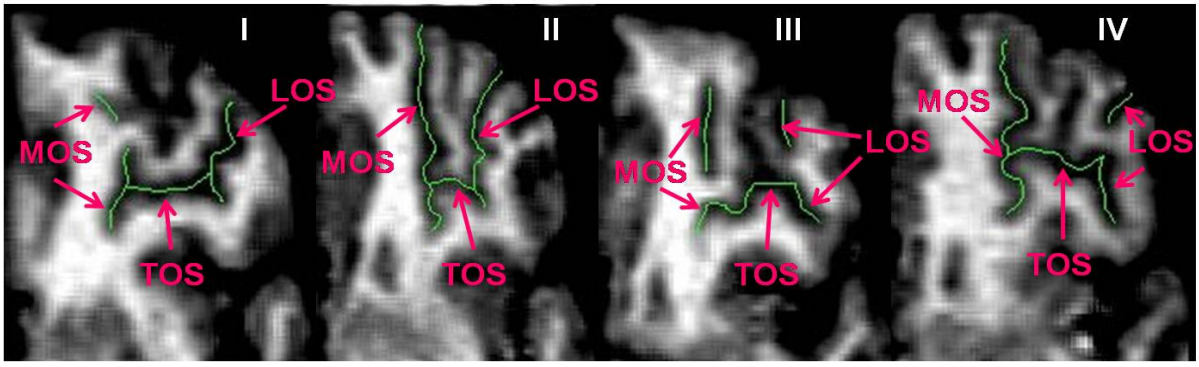
Despite the known inconsistency of orbitofrontal sylcogyral morphology, Chiavaras and Petrides (2000) developed a classification by which orbitofrontal sulcogyral patterns could be separated into three types based on connectivity of the two main orbital sulci: medial and lateral orbital sulci through the third one - transverse orbital sulcus. In type I the rostral part of lateral orbital sulcus is connected with the caudal part of lateral orbital sulcus through transverse orbital sulcus while the rostral and caudal parts of medial

orbital sulcus are disconnected. The type II, which is commonly described as 'H - shaped' pattern (Williams *et al.,* 1989), is formed by the union of the lateral, medial and transverse orbital sulci. The type III is characterized by parting of the rostral and caudal portions of both medial and lateral orbital sulci.

Chiavaras and Petrides (2000) reported the prevalence of type I in a healthy population (identified in 56% of hemispheres) with the minority of two other types: type II was seen in 30% of hemispheres while type III appeared in 14% of hemispheres only. The variability even within each type was described as considerable. Later Nakamura and colleagues (2007) reported alteration of orbitofrontal cortical folding patterns in patients with schizophrenia with increased type III and reduced type I in the right hemisphere. It was also notable that possession of type III in patients with schizophrenia was associated with poorer socioeconomic status, more severe psychotic symptoms and more severe cognitive impairment when compared with patients of any other orbitofrontal pattern. Distribution of orbitofrontal sulcogyral types in other diagnostic groups was not previously estimated.

Chiavaras and Petrides (2000) formulated the method of orbitofrontal anatomical classification on healthy volunteers. Therefore, it is possible that in ill or at risk to develop psychiatric illness populations disease related patterns emerge which are not accommodated by Chiavaras' classification.

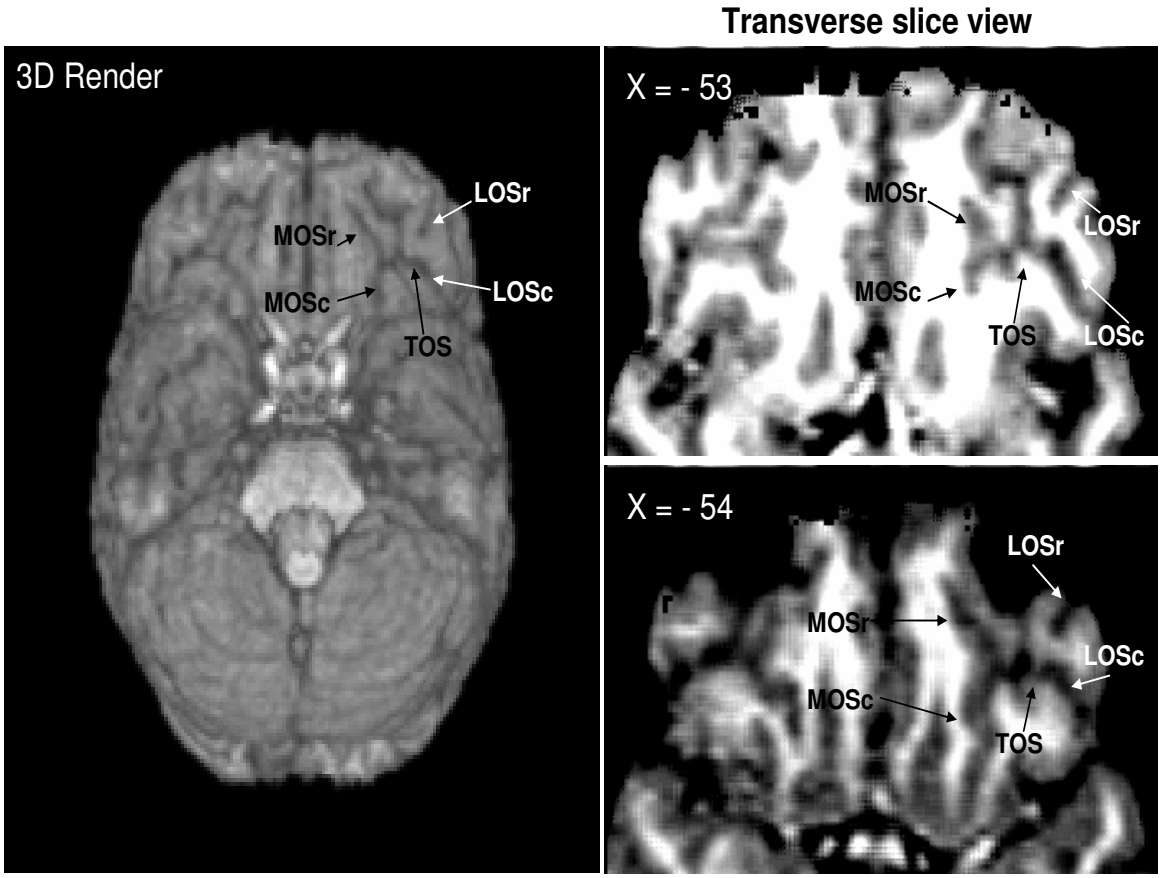
Figure 1.4. Orbitofrontal sulcogyral patterns. Images have been created by delineating sulci on the transverse view of MRIcro software. The orbitofrontal cortex (OFC) sulci of interest are: LOS = Lateral Orbital Sulcus; MOS = Medial Orbital Sulcus; TOS = Transverse Orbital Sulcus. The orbitofrontal patterns: I = type I, II = type II, III = type III, IV = type IV. All four types are demonstrated using the left hemisphere of four different participants.



1.2.4.3.2 Type IV (See Figure 1.4 and 1.5)

Type IV was identified for the first time in the Edinburgh High Risk Study (Chakirova *et al.,* 2010) and was described as the orbitofrontal pattern with the rostral and caudal portions of the medial orbital sulci have been connected through the transverse orbital sulcus and the rostral and caudal portions of the lateral orbital sulci have been disconnected.

Figure 1.5. An example of the orbitofrontal type IV on 3D Render and transverse slice viewer. LOSr = the rostral part of the lateral orbital sulcus; LOSc = the caudal part of the lateral orbital sulcus; MOSr = the rostral part of the medial orbital sulcus; MOSc = the caudal part of the medial orbital sulcus; TOS = transverse orbital sulcus. This image was obtained using MRIcro software.



1.2.5 Connections of the orbitofrontal cortex (See Figure 1.6)

The orbitofrontal cortex is widely connected with different brain regions such as the amygdala (Amaral and Price, 1984; Carmichael and Price, 1995 a),

insula (Mesulam and Mufson, 1982), cingulate cortex (Van Hoesen *et al.,* 1993), premotor area (Rizzolatti *et al.,* 1988; Barbas and Pandya, 1989; Morecraft *et al.,* 1992), prefrontal regions (Barbas and Pandya, 1989; Carmichael and Price, 1995b), hypothalamus (Rempel - Clower and Barbas, 1998), hippocampus (Cavada *et al.,* 2000), the mediodorsal thalamic nucleus pars magnocellularis (Ongur and Price, 2000) and the striosomal compartment of the anterior and ventromedial striatum, mainly the caudate nucleus (Eblen and Graybiel, 1995). The pathway between the orbitofrontal cortex and striatum may control dopaminergic substantia nigra pars compacta neurons and therefore influence the behaviour (Rolls, 1999 a). The orbitofrontal cortex also receives input from all the sensory modalities: gustatory, olfactory, somatosensory, auditory and visual (Rolls, 1999 a, b). It innervates by cholinergic and aminergic subcortical fibres (Morecraft *et al.,* 1992). Moreover, the cholinergic innervation of orbitofrontal cortex arrives from the nucleus basalis of Meynert, and the orbitofrontal cortex projects into the nucleus basalis. This means that the orbitofrontal cortex can potentially control cholinergic input to the entire cerebral cortex (Mesulam and Mufson, 1984).

There are important differences in a way the lateral and medial regions of the orbitofrontal cortex are connected to the other brain areas. Evidence suggests that the lateral part of the OFC is connected with sensory areas of the somatic, visual and gustatory modalities, insular cortex, inferior temporal cortex (Cavada *et al.,* 2000), anterior cingulate cortex, entoperirhinal cortex, dorsolateral prefrontal cortex (DLPFC), ventromedial parts of the basal nucleus of amygdala, ventromedial parts of mediodorsal thalamic nucleus (Carmichael and Price, 1995 a, b), premotor cortex (Cavada *et al.,* 2000), and parietal cortex (Carmichael and Price, 1995 a, b). The medial part of the orbitofrontal cortex is connected with posterior cingulate cortex, ventrolateral parts of the basal nucleus of the amygdala (Carmichael and Price, 1995 a, b), posterior parahippocampal cortex, the hippocampus, posterior

retrosplenial area, area prostriata (Cavada *et al.,* 2000), DLPFC, and dorsomedial parts of mediodorsal thalamic nucleus (Carmichael and Price, 1995 a, b).

Figure 1.6. Connections between the orbitofrontal cortex and other major regions in the human brain. IT = the inferior temporal cortex; TE = the ventrolateral surface of the inferior temporal cortex.

Further, isocortical and non-isocortical parts of the orbitofrontal cortex receive inputs from different functional areas of the brain based on the

cytoarchitectonical organization (Morecratf *et al.,* 1992). The non-isocortical (agranular and dysgranular) orbitofrontal cortex tends to receive inputs from non-isocortical brain areas including primary gustatory and olfactory areas (Cavada *et al.,* 2000), hippocampus, amygdala, midline thalamic nuclei, non-isocortical parts of paralimbic areas (Morecratf *et al.,* 1992) and non-isocortical temporal lobe (Cavada *et al.,* 2000). Similarly, the isocortical granular orbitofrontal cortex receives inputs from the isocortical brain areas including sensory areas of the somatic, visual and auditory modalities, isocortical premotor area (Cavada *et al.,* 2000), the granular insula, granular temporal pole, dorsolateral prefrontal cortex, posterolateral temporal cortex, the medial dorsal and pulvinar thalamic nuclei (Morecratf *et al.,* 1992).

1.2.5.1 Sensory inputs

The orbitofrontal cortex receives inputs from the cortical areas associated with the olfactory (Carmichael *et al.,* 1995b; Price, 2003), taste, visceral afferents, somatic sensation and visual sensory systems. Additionally, the orbitofrontal cortex is involved in food assessment (Rolls, 2005). Moreover, the orbitofrontal neurons respond not only to the sensory characteristics of the stimuli but also to their affective characteristics (Schultz *et al.,* 2000). Importantly, the orbitofrontal cortex seemed to be connected with the ventrolateral prefrontal cortex (Petrides, 2005). Both these areas are known to receive multiple sensory inputs.

The posterior part of the OFC (including the agranular insular and adjacent orbital cortices) receives olfactory sensory information from the primary olfactory cortex (Tanabe *et al.,* 1975 a, b; Price, 1985; Carmichael *et al.,* 1995 b). Axons to the orbitofrontal area arise from the anterior olfactory nucleus, piriform cortex and from some parts of the periamygdaloid cortex, and terminate in areas adjacent to the olfactory cortex, extending to other agranular insular areas and BA 13. These axons end mostly in the layer I,

extending deeper in to the cortical layers only in areas adjacent to the olfactory cortex. Moreover, projections from the olfactory cortex go to the medial part of the mediodorsal nucleus of the thalamus. The thalamus projects further to the orbitofrontal cortex (Heimer, 1972; Krettek and Price, 1977; Russchen *et al.,* 1987; Ray and Price, 1992, 1993). Several areas of the olfactory cortex send their axons to the orbitofrontal cortex including piriform cortex, anterior olfactory nucleus, and the periamygdaloid cortex. Some of these fibers terminate in layer I of the BA 1, while the others extend to the BA 13 and agranular insular areas. More rostral parts of the orbitofrontal cortex participate in the integration of the sensory information from different sensory modalities using the connection of the orbitofrontal network.

The orbitofrontal cortex receives visual information from the ventral visual association stream in the inferior temporal cortex, including the ventral temporal pole, TEO (temporal occipital area) and the anterior ventral part of the TE (Seltzer and Pandya, 1978; Webster *et al.,* 1994; Carmichael and Price, 1995b; Batardiere *et al.,* 2002; Kondo *et al.,* 2003). Area TE of the inferotemporal cortex is thought to be a final stage of the occipito - temporal pathway that was previously found to be important for visual object recognition (known as visual association area) (Tanaka *et al.,* 2003; Borra *et al.,* 2009). The anterior ventral part of the TE and the ventral temporal pole are connected to all the areas of the orbital network (Kondo *et al.,* 2003), while more caudal areas are connected to BA 47/12 and BA 45 (Carmichael and Price, 1996). Areas 47/12 and 45 have been found to be related to the object memory function (Wilson *et al.,* 1993; Romanski, 2004). The ventrolateral prefrontal cortex is found to be associated with higher level of sensory processing, including the selection of the object, its comparison and judgement (Petrides, 1996; Passingham *et al.,* 2000; Petrides, 2005).

The nucleus of the solitary tract passes taste and visceral information to the medial parvicellular part of the ventroposterior medial nucleus of the thalamus (Beckstead *et al.,* 1980) from where the information goes to the cortex in the anterior insula. The dorsal part of the nucleus projects mainly to the primaty taste cortex in the dorsal part of the insula. The agranular insular area receives inputs from the cells in the ventral lamina of the taste/visceral - associated thalamic nucleus. The dorsal lamina of the same thalamic nucleus receives input from the anterior part of the solitary tract.

1.2.5.2 Limbic connections

The orbitofrontal cortex is found to be connected to a number of limbic structures, including the amygdala, hippocampus, entorhinal cortex and parahippocampal gyrus. Most of these areas are connected to the medial prefrontal network (the medial edge and caudolateral part of the orbitofrontal cortex). There are an agranular insular area in the caudal part of the orbital network and the perirhinal cortex that also have limbic connections.

1.2.5.3 Outputs to hypothalamus and midbrain

The medial prefrontal network is widely connected with the hypothalamus and midbrain (An *et al.,* 1998; Ongur *et al.,* 1998; Rempel - Clower and Barbas, 1998; Freedman *et al.,* 2000). The projections to the hypothalamus go from areas 25, 32 and from the caudolateral orbital areas 1 and 47/12 (Ongur *et al.,* 1998). The distribution of the fibers from the medial prefrontal cortex suggests that it influences endocrine and autonomic functions of the hypothalamus. The lateral hypothalamus receives projections from the BAs 1, 47/12 and 13 of the medial network and from the agranular insular area I of the orbital network (Ongur *et al.,* 1998). So, the medial and lateral hypothalamus receives different projections from distinguishable parts of the medial network and, therefore, might play different roles in visceral control.

From the hypothalamus many projections continue caudally into the tegmentum and ventral midbrain, and then to the PAG (An *et al.,* 1998; Ongur *et al.,* 1998). Strikingly, many of the axons from the medial network are predisposed to aggregate around the serotonergic cells of the median raphe and the cholinergic cells of the peripeduncular pontine tegmental nucleus. These axons also appeared to form a moderate terminal area within the ventral tegmental area and the pars compacta of the substantia nigra (An *et al.,* 1998; Ongur *et al.,* 1998; Freedman *et al.,* 2000). Freedman and colleagues (2000) reported that axons from BA 25 were found enfolding a group of tyrosine hydroxylase immunoreactive cells that were located in the lateral parabrachial nucleus of pons.

1.2.5.4 Thalamic and striatal connections

The orbitofrontal cortex is also found to be connected to the thalamus and striatum, particularly to the medial, magnocellular parts of the mediodorsal nucleus, anterior thalamic group, several midline and intralaminar nuclei, and medial pulvinar (Cavada *et al.,* 2000). Some of these regions target the medial network, while the others target the orbital network. For example, the dorsomedial and dorsocaudal parts of the mediodorsal nucleus are connected to the medial network, while the ventromedial area of the nucleus is connected to the orbital network.

Within the striatum, the ventromedial or 'limbic' striatum, including the rostromedial caudate nucleus, nucleus accumbens and ventral putamen receives inputs from the medial network. A more central part of the striatum receives inputs from the orbital network, including BAs 11, 47/12, and 13.

1.2.5.5 Conclusion

In conclusion, the orbitofrontal cortex could be separated into two distinct networks: the orbital and medial prefrontal networks that were defined on the basis of their intrinsic cortico - cortical connections.

The orbital network receives its inputs from sensory modalities, linking the orbitofrontal cortex to the insula, the sensory association cortex in the inferior temporal lobe, taste and visceral cortical areas, and the primary olfactory cortex.

The medial network includes such areas as a caudolateral orbital region and the gyrus rectus (localised on the medial edge of the orbitofrontal cortex). This network projects outputs to the brainstem and hypothalamus (the visceral controls structures). It is also connected with such limbic areas as the entorhinal cortex, hippocampus, and amygdala, as well as the parahippocampal cortex, the rostral part of the superior temporal lobe, and the posterior cingulate and retrosplenial cortex.

The neurons of the orbital network were found to be associated with the sensory function, reward and other affective aspects of stimuli. The neurons of the medial network are involved in mood, emotional behaviour and the cortical modulation of visceral function.

1.2.6 Neurochemical modulation of orbitofrontal cortex function

Numerous neurotransmitter systems modulate neurotransmission within the orbitofrontal cortex including serotonergic (Young *et al.,*1994; Way *et al.,* 2007; Rosell *et al.,* 2010), dopaminergic (Moghaddam, 2002; Calaminus and Hauber, 2008; De Almeida and Mengod, 2010; Lodge, 2011), noradrenergic (Jodo *et al.,* 1998), cholinergic (Roberts *et al.,* 1992; Everitt and Robbins,

1997; Himmelheber *et al.,* 2001; Hasselmo and Sarter, 2011), glutamatergic (Moghaddam, 2002; Miguel-Hidalgo *et al.,* 2010), GABAergic (De Almeida and Mengod, 2010), norepinephrinergic (Young *et al.,*1994), glucocorticoid and peptidergic (corticotrophin-releasing factor function) (Carrol *et al.,* 1981; Young *et al.,* 1993; Catapano and Manji, 2007). Some of them like dopaminergic and glutamatergic neurotransmitter systems are associated with schizophrenia, while serotoninergic and norepinephrinergic neurotransmitter systems are related to bipolar affective disorder.

a). The orbitofrontal cortex is one of the regions implicated in the regulation of the dopaminergic system (Lodge, 2011). Evidence from the recent studies suggests that the orbitofrontal cortex activation may result in inhibited activity of the dopaminergic neurons within the ventral tegmental area (Moghaddam, 2002).

Dopamine is known as the primary monoamine inhibitory neurotransmitter (catecholamine). Dopamine is synthesized from tyrosine which enters from the brain extracellular fluid into dopaminergic neurons where tyrosine is converted to dihydroxyphenylalanine (L-DOPA) by the cytosolic enzyme tyrosine hydroxylase (Holzbauer *et al.,* 1983 a, b). After that the cytosolic enzyme aromatic amino acid decarboxylase (AADC or dopa decarboxylase) decarboxylates L-DOPA to dopamine.

There are five subtypes of dopamine receptors: $D_{1\text{-}5}$. The D_1 and D_5 receptors are members of the D_1-like family of dopamine receptors, whereas the D_2, D_3 and D_4 receptors are members of the D_2-like family. D_1 and D_2 are two primary dopamine receptor-types: D_1 – stimulatory and D_2 – inhibitory (Bartholomeusz *et al.,* 2003). Within the prefrontal cortex D_2 receptors are mainly expressed in layer V, while D4 receptors could be found in all layers of the prefrontal area with an exception of layer I (De Almeida and Mengod, 2010). Both D_1 and D_2 operate through G-proteins. D_2-receptors were named

autoreceptors as they are able to inhibit both synthesis and release of dopamine. These receptors are also known as modulatory as they can provide a negative feedback (Bartholomeusz *et al.,* 2003; Dalley and Roiser, 2012).

According to Slopsema and colleagues (1982) the distribution of the dopaminergic receptors throughout the frontal lobe differs with the orbitofrontal and medial prefrontal cortices having 3 and 4 times higher the level of dopaminergic receptors respectively when compared to non-prefrontal areas of the frontal lobe. Moreover, there is a lateralisation of the dopaminergic receptors' distribution that appears to be significantly higher in the left hemisphere (Slopsema *et al.,* 1982).

The dopaminergic system also includes four main dopaminergic tracts: the nigrostriatial tract, tuberoinfundibular tract, mesolimbic tract and mesocortical tract. The nigrostriatial tract connects the substantia nigra and the striatum and accounts for most of the brain's dopamine and controls voluntary movement. The tuberoinfundibular tract runs from the arcuate nucleus of the hypothalamus to the pituitary stalk. It has a controlling effect on the release of the hormone prolactin through tonic inhibition via D_2-receptors. The mesolimbic tract starts from the ventral tegmental area and goes to many parts of the limbic system. The mesocortical tract connects the ventral tegmental area and the neocortex, particularly the prefrontal area. It is known that the midbrain dopamine system is involved in regulation of motor activity, motivation and reward pathways. A crucial role of the mesolimbic dopamine system is its play in goal-directed behaviour.

There are two theories of the development of schizophrenia which concern dopamine. According to the pathogenic theory an overstimulation of D_2-receptors in the mesolimbic and mesocortical systems plays an important role in the development of schizophrenia. The 'excess dopamine' theory of

schizophrenia largely based on evidence that antipsychotics, D_2-antagonists drugs, reduce the symptoms, whereas amphetamines, substances increasing D_2-stimulation, are able to induce psychotic symptoms (which could be reversed with D_2-antagonists).

Regulation of the dopaminergic activity by the orbitofrontal cortex could be linked to the other neurotransmitter systems. For example, evidence suggests that in the orbitofrontal cortex the dopamine transporter binding was found to be inversely correlated with the serotonin transporter binding (Nakamura *et al.,* 2010). Further, evidence from anatomical studies suggests that the orbitofrontal cortex modulates activity of the ventral tegmental area directly or indirectly (Gabbott *et al.,* 2005). Moreover, the majority of the dopaminergic neurons in the ventral tegmental area can be regulated (an inhibitory effect) by the OFC (Lodge, 2011). Furthermore, this regulation is secondary to the GABA neurons activity that is more likely to have an origin within the ventral tegmental area or nucleus accumbens (Lodge, 2011).

The way the orbitofrontal cortex regulates dopaminergic activity differs from that of the medial prefrontal cortex (Lodge, 2011). OFC inhibits dopaminergic activity while the medial prefrontal cortex activates dopaminergic neurons creating a positive feedback loop consisting of layer 5 pyramidal neurons of the medial prefrontal cortex, dopamine itself and D_2–like receptors (Lodge, 2011).

b). Glutamate is known as the major excitatory neurotransmitter in the human brain. The role of glutamate is in regulating the threshold for excitation of most other neurotransmitter systems. It could also result in excitotoxicity (the capacity for destroying neurons) when released in excessive amounts. Both a ligand (glutamate) and a voltage are involved in regulation of the glutamate's NMDA-receptors with at least five binding sites for glutamate, glycine, magnesium, zinc and a site that binds the hallucinogenic substance

phencyclidine (PCP, 'angel dust'). The glutamate's NMDA-receptors are concentrated most densely in hippocampus (especially in the CA1 region), amygdala, and basal ganglia. The pathogenic theory of schizophrenia suggests that reduced activation of NMDA receptors in the brain could be a reason of the disorder. This theory is connected to the dopaminergic theory of schizophrenia as activation of NMDA receptors of the orbitofrontal cortex decreases activation of dopaminergic neurons (Lodge, 2011). Moghaddam (2002) suggested that activation of cortical dopamine is regulated by glutamatergic neurotransmission within the ventral tegmental area, the prefrontal cortex, or both.

c). Serotonin system – 5-HT-receptors (indolamine)

Serotonin is one of the many neurochemical influences that impact the functioning of the orbitofrontal cortex (Way *at al.,* 2007). It is known to be one of the primary monoamine neurotransmitters. However, only 1-2% of the serotonin in the body is located in the brain. This substance is widely distributed in platelets, mast cells, etc. It is also known that serotonin in the brain is synthesized from tryptophan, firstly, by hydroxylation (by enzyme tryptophan hydroxylase) into 5-hydroxytryptophan (Gottfried and Riesgo, 2011). Secondly, the latest is decarboxylated (by enzyme aromatic L-amino acid decarboxylase) into serotonin or 5-hydroxytryptamine (5-HT) (Gottfried and Riesgo, 2011) and transported across the blood - brain barrier and that there is no equilibration between body serotonin and brain serotonin.

The distribution of the serotoninergic receptors within the orbitofrontal cortex is organised according to its cytoarchitectonic structure (Way *et al.,* 2007). The gradient of the distribution of the serotoninergic receptors decreases from the caudal to rostral orbitofrontal cortex and from medial to lateral (within the agranular and dysgranular areas) orbitofrontal cortex (Way *et al.,* 2007). Therefore, the caudomedial orbitofrontal cortex has the highest

density of the serotoninergic receptors, while the rostral and granular lateral areas have the lowest density of the serotoninergic receptors.

The neurons that produce the serotonin neurotransmitter are mainly found in the raphe nuclei. According to Roberts (2011), the dorsal raphe nucleus is the major contributor to a serotonin innervation of the orbitofrontal cortex with smaller contribution coming from the medial raphe nucleus. Importantly, the reciprocal innervation from the orbitofrontal cortex allows the regulation of the 5-HT inputs of the entire forebrain by the OFC (Roberts, 2011).

Serotonin is mainly concentrated in the pineal body, even though the pineal gland does not employ serotonin as a neurotransmitter. Serotonin is used for synthesis of melanin, the substance which can darken the skin of amphibians – although it has also been reported to induce pigment lightening in cells. Melatonin is involved in regulating diurnal (circadian) and seasonal behaviour and physiology in mammals which means that activity of the pineal gland is influenced by light. This is why the pineal body has been called a 'third eye'. In the darkness, norepinephrine stimulates pineal cells. This leads to release of cyclic AMP second messenger, which phosphorylates the N-acetyl transferase enzyme. This enzyme catalyzes acetylation of serotonin. There is some evidence that serotonin might be involved in dreaming as during dreaming electrical activity in the visual cortex might arise from the brain stem and not from the eyes.

Evidence suggests that serotonin might be associated with aggression, suicidal behaviour, anxiety and affective disorders. Cases of patients with low serotonin levels who have attempted suicide support an involvement of serotonin in anxiety and impulsive behaviour. Moreover, evidence from different PET, 5-HT receptor binding, neuroendocrine, peripheral cell, and cerebrospinal fluid studies suggest that serotoninergic system might be involved in depression (Goodwin and Jamison, 2007). Further, the

orbitofrontal cortex is the main area that was reported to be associated with therapeutic response to 5-HP transporter inhibition in impulsive-aggressive and obsessive-compulsive disorders (Saxena et al., 1999; New et al., 2004). Rosell and colleagues (2010) found increased availability of the orbitofrontal serotoninergic receptors in patients with impulsively aggressive personality disorder with current physical aggression compared to patients without current physical aggression and healthy participants.

Further, Clarke and colleagues (2007) showed that impairment of the orbitofrontal serotoninergic innervation affected the performance during orbitofrontal cortex – associated cognitive tasks. Groman and colleagues (2013) reported functional interaction between levels of the orbitofrontal serotonin and putamen dopamine that might explain at least some variability in individual reversal learning performance. The complex relationship between these two monoamine systems might be associated with the inhibiting function of the orbitofrontal cortex (Groman *et al.,* 2013). When the putamen dopamine level is low, the low orbitofrontal cortex serotonin level was associated with poor reversal learning performance. When the putamen dopamine level is increased, the low orbitofrontal serotonin level was associated with the improved reversal learning performance (Groman *et al.,* 2013).

Moreover, Catalano (2001) suggested modulatory effect of serotonin on the plasticity and function of the adult brain. Furthermore, it might also play a role in maturation of the specific regions in the developing brain (Whitaker-Azmitia, 2005).

d). Norepinephrine system (NE-receptors)

Norepinephrine is another example of primary monoamine (or catecholamine) neurotransmitters. The synthesis of norepinephrine starts

from dopamine using the enzyme dopamine beta - hydroxylase and oxygen, copper and vitamin C as co-factors. According to animal studies over 40% of noradrenergic neurons is localised in locus ceruleus in the pons. The other large region of the noragrenergic neurons distribution is the lateral tegmental area. The locus ceruleus sends the noradrenergic stimulation to the neocortex, hippocampus and cerebellum. The lateral tegmental nuclei send the dopaminergic innervation to the hypothalamus. Stress conditions may increase brain norepinephrine turnover. Goodwin and Jamison (2007) reported that in mania an increase in noradrenergic function has been observed consistently.

1.2.7 The neurophysiology and function of the orbitofrontal cortex

Known as multifunctional area, the orbitofrontal cortex appeared to be important in sensory-visceral multimodal integration, hedonic experience and the processing of emotions (Ongur and Price, 2000; Kringelbach, 2005). It was established that the orbitofrontal region is involved in such executive functioning as motivation, decision-making and goal-directed behaviour (Walton *et al.,* 2004), also in the affective evaluation of the reinforcements such as rewards and punishments (Holland and Gallagher, 2004). Cytoarchitectonicly the orbitofrontal cortex was subdivided into five subregions: area 10 at the frontal pole, 11 anteriorly, 47/12 laterally, 13 caudally and 14 medially (Barbas and Pandya, 1989; Carmichael and Price, 1994; Petrides and Pandya, 1994). Therefore, it is possible that there are some functional differences between these subregions of the orbitofrontal area. Emerging evidence supports this idea as it was discovered that medial orbitofrontal cortex activity is linked with the monitoring of reward value while the lateral orbitofrontal cortex is associated with the evaluating of punishing value. The medial part of the orbitofrontal cortex was found to be involved in 'pure' emotional processing, especially for negative emotions, while the lateral region of the OFC is linked to formation of associations between

cognition and emotions, especially positive emotions (Baker *et al.,* 1997; Drevets *et al.,* 1998; Northoff *et al.,* 2000). The anterior region of the orbitofrontal cortex associates with more complex or abstract reinforcers while the posterior region deals with such simple reinforcers as taste or pain (Kringelbach and Rolls, 2004). There is also evidence of personality traits mediated by the lateral orbitofrontal cortices: neuroticism by the left lateral orbitofrontal cortex and introvertism by the right orbitofrontal cortex (Fujiwara *et al.,* 2008).

Moreover, the orbitofrontal cortex may play an important role in encoding and retrieving episodic memories, including particularly autobiographic – episodic memories. This could be explained by the emotional and self-related nature of those memories. Evidence suggests that the lateral and medial parts of the prefrontal brain region might be differently engaged in the processing of such memories. The medial part was found associated to positive memories while the lateral part was linked to negative memories (Cavada *et al.,* 2000; Markowitsch *et al.,* 2003).

1.2.8 The lateral orbitofrontal cortex and the inhibitory control of emotions

The neural basis of emotional processing via inhibition may be investigated through such feelings as sadness, anger, general negativity and sexual arousal (Beauregard *et al.,* 2001; Blair, 2001; Levesque *et al.,* 2003). There is evidence that the orbitofrontal cortex play a role in the executive control of information processing and behavioural expression by inhibiting neural activity that is found to be associated with unwanted, irrelevant or uncomfortable information, sensations, or actions (Shimamura, 2000). Specifically, the lateral orbitofrontal cortex was found to be implicated in strategies that were employed to reduce negative affect.

A number of research studies indicated an important role of the orbitofrontal cortex in the processing of facial expressions. Strikingly, an involvement of the orbitofrontal cortex in the processing of negative facial expressions seems to be greater than of positive facial expressions (Iidaka *et al.,* 2001; Ruffman *et al.,* 2008).

1.3 Neuropsychological assessment of the orbitofrontal cortex

A number of tasks were developed to assess multiple functions of the orbitofrontal cortex. The mostly known of the tasks are the Wisconsin Card Sorting Task, the ID/ED task of the CANTAB (CAmbridge Neuropsychological Test Automated Battery), the Object Alternation Paradigm, Event-related fMRI task (Cambridge), the go/no-go tasks, Decision-making (gambling) tasks, Social processing and a Theory of Mind.

1.3.1 The Wisconsin Card Sorting Task

The sorting task was initially developed by Ach in 1900 (Nyhus and Barceló, 2009). In this first version participants had to sort cards with non-sense words on the basis of some common characteristics that were shared by the word represented objects. In 1920 the sorting task was used to examine brain-damaged patients for concrete and abstract thinking by Goldstein (Nyhus and Barceló, 2009). In 1948 the Wisconsin Card Sorting Test (WCST) was devised by David A. Grant and Esta A. Berg (1948) as the one of 'set-shifting' neuropsychological tasks which is usually applied to test someone's abstract reasoning, strategies and concept formation as a response to changing contextual contingencies. Currently there many versions of administration and scoring of the Wisconsin Card sorting Test including the standard version (Grant and Berg, 1948) with Milner's correction criteria (1963) and modified version by Nelson (1976). The conventional form of the WCST (Heaton, 1981) consists of 128 response cards with geometric figures and

four ‘key’ cards. The geometric figures vary according to three dimensions such as colour, shape and number. During the task the participant is presented with a set of cards containing stimuli which are different in colour, shapes and number of them in each card. The participant is also given an additional card which he is asked to match to any of the cards from the set. Before presenting the additional card the investigator decides whether the cards are to be matched by number, shape or colour (creating the rule). The participant is unaware of the rule and is supposed to guess. Once the participant chooses the right rule, he has to maintain this sorting principle ignoring other stimulus dimensions. The investigator informs the participant whether the match was correct or incorrect. When participant discovers the rule the investigator changes it into a new one and estimates the time necessary for the participant to learn the new rule and scores the total amount of mistakes made during this learning process. The rules are changed a number of times during the WCST in order to fully comprehend the participant’s abilities to shift his attention. Most commonly used scores in this test include number of categories completed, number of perseverative errors, and number of non-perseverative errors.

The WCST is usually applied by psychiatrists, neurologists, clinical psychologists and neuropsychologists to patients with neurodegenerative disorders, brain injuries or mental illnesses such as schizophrenia or bipolar affective disorder. The Wisconsin Card Sorting Test was reported by some studies to be sensitive to frontal lobe impairment and considered as a measure of executive function. However, this task was declared as providing with the assessment of many cognitive functions including motivation, strategic planning, organized searching, analyzing the feedbacks to cognitive set-shifting choice, goal - directing behaviour and modulating impulsive responses. Given that, it is important to note that in order to complete this test successfully other cognitive functions including visual processing, visual

discrimination, working memory and ability to maintain and shift attention must be intact.

A number of brain lesion studies have investigated the specificity of neuropsychological tests to the frontal lobe function including an examination of the executive function using the Wisconsin Card Sorting Test (WCST). Despite the claimed sensitivity to the frontal lobe dysfunction patients with the non-frontal brain lesions can also perform poorly during the WCST (Nyhus and Barcelo, 2009).

1.3.2 The Object Alternation Paradigm

This is a description of the computerized version of the WCST task that was designed to be as similar as possible to the original task given in Freedman (1990). Besides the use of computer interface, the two versions differ mainly in the substitution of material rewards for verbal reinforcement. In a computerized version of the object alternation paradigm two red squares presented on the computer screen. An investigator usually asks a participant to guess whether the Spanish word ‘bien’ (means ‘All right’) is hidden under the first or the second square. The participant chooses a square on the computer screen by pressing with the mouse cursor. According the task design on the first trial word ‘bien’ can appear under either of the squares. However, for all the rest of the trials, positive feedback will appear on the screen only when the participant will shift to the square he did not choose previously. So, the positive feedback remains under the same square until it is selected. Hence, if the participant chooses the same square consecutively, there will be no positive feedback appearance on the screen. Two or more consecutive incorrect decisions prior to changing strategy were defined as a perseveration. The maximum total number of trials in this task is twenty five. However, the task can be completed and terminated as soon as the

participant accomplishes fifteen correct decisions. There was an interstimulus gap of five seconds between trials.

1.3.3 The ID/ED task (CANTAB)

The ID/ED task of the CANTAB represents a computerized version of the Wisconsin Card Sorting test and is usually applied to patients with schizophrenia, Parkinson's disease and bipolar affective disorder.

The Intra-dimensional – Extra-dimensional (ID/ED) task from the CANTAB battery consists of nine stages, including simple discrimination, reversal of simple discrimination, two compound discrimination stages, reversal of compound discrimination, intra-dimensional set-shifting stage, reversal of intra-dimensional set-shifting, extra-dimensional set-shifting and reversal of extra-dimensional set-shifting. Two sets of stimuli are used in this test: colour-filled shapes and white lines. Only one of these dimensions is present during the simple discrimination stage, whereas white lines overlie colour-filled shapes at the compound discrimination. The participant discovers the rule by touching chosen stimulus on the screen and receiving a feedback. After six correct responses the stimuli, the rule or both are changed. If participant fails to identify the rule after 50 trials, the test terminates.

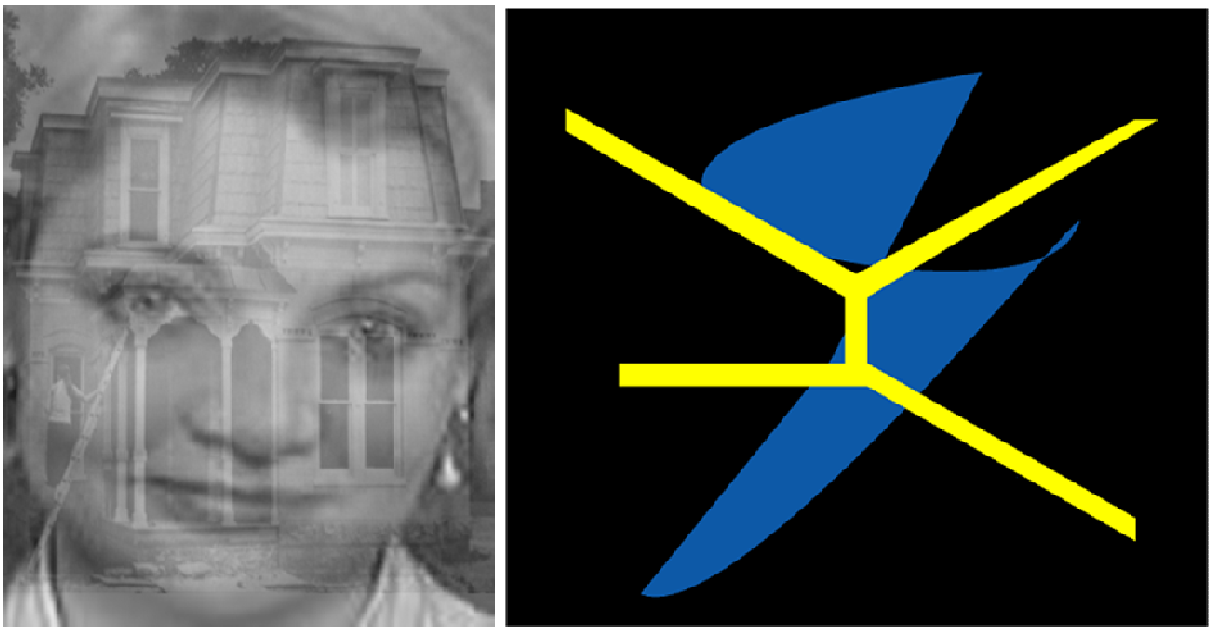
1.3.4 Event-related fMRI task (Cambridge)

This task was used in the experiment described in **Chapter 2** of this thesis (See **Chapter 2**, p. 55). The participants were told that they would be shown two pairs of pictures and they had to guess which part of each picture was "the target" and, when they were told they were correct, they should keep choosing that until the pictures changed or until they were told that they were incorrect, and then they would have to guess which was the new target. They

were told that they would not get feedback after every choice, so they must chose the same picture twice to find out if they were correct.

Two varients of compound stimuli were used. In the first version of the task, the stimuli were the same as used by Hampshire and Owen (2006): namely, mono-chrome photographs of faces and buildings which were overlaid using a transparency tool. In the second version of the task, the stimuli were blue abstract shapes with yellow lines superimposed, which were created to resemble stimuli as used in the CANTAB® ED/ID task (Cambridge Cognition, Cambridge UK). The stimuli, whether faces/buildings or shapes/lines, were always presented in a pair, with each stimulus being a composite of one (different) exemplar from each stimulus dimension (See **Figure 1.7**).

Figure 1.7. Examples of the stimuli used in the event-related fMRI task.



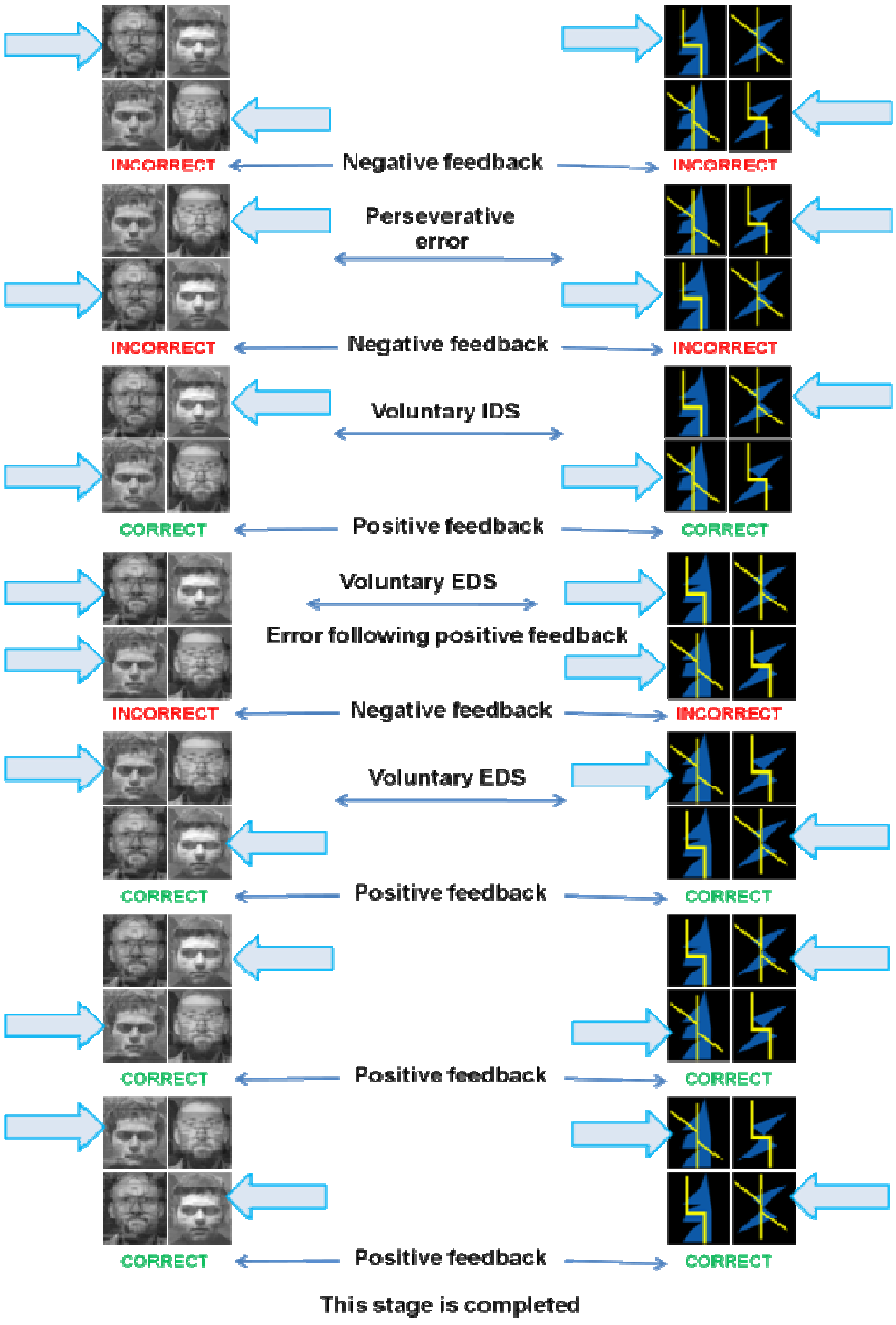
A “trial” was defined as two sequential presentations of pairs of compound stimuli, the first presentation being one configuration of the two stimulus dimensions and the second presentation being the alternate configuration. That is to say, if the first pair were Building 1/Face A with Building 2/Face B, the next pair presented would be Building 1/Face B with Building 2/Face A. The participant chose one stimulus in each of the two sequentially presented pairs and was then given feedback, which would complete the trial. For each pair presented, the participants were required to indicate the location of the ‘target’ element on the left or the right of the screen using the arrow keys on the keyboard. The stimuli stayed on the screen until the participant responded, after which they disappeared from the screen. Because of the orthogonal configuration of the stimuli, it was possible to identify which particular component of the compound stimuli was selected on both of the two pairs comprising a trial. If the target was selected on both choices in a trial, then the feedback was the word ‘CORRECT’ in green, otherwise,

feedback was the word 'INCORRECT' in red. After 3 consecutive correct trials (that is to say, the target component was selected 6 times in a row, with positive feedback for every other choice), the "stage" was complete. The next stage began with a new target and the participant had to discover once again which was the correct target. The participants were instructed to "try to respond as quickly and accurately as possible" and to respond consistently to the correct target until the stimuli changed or until they received feedback that it was now incorrect.

Each new stage was one of four conditions: there would be either a 'Stimulus Change', which replaced all the previous stimulus exemplars with new stimulus exemplars, although the characteristics of the stimuli (faces/buildings or shapes/lines) would not change within a block. Alternatively, there could be a 'Contingency Change', wherein the target stimulus would be reassigned but the particular stimulus exemplars would remain the same. Within each of these conditions, there could be an intradimensional shift (IDS), where the new target was from the same stimulus dimension, or an extradimensional shift (EDS), where the new target was from the alternate stimulus dimension. The stages when the new target was from the same category (IDS) and the stimuli did not change (a Contingency, rather than a Stimulus, Change) are examples of reversal learning: that is to say, the previous target was now a non-target and the previous non-target the new target. Within each stage, the participant has to discover the target identity and respond consistently to the target, with the criterion for resolving the stage being 3 correct trials (i.e., consistently selecting the target 6 times). However, they are permitted no more than 15 trials in order to resolve the stage: if, after 12 trials, they do not then perform 3 correct trials, that stage is recorded as failed and a new stage begins. In the new stage, the target always changed, but it could be a Stimulus or Contingency change and it could also be an IDS or an EDS, with equal probability. **Figure 1.8** shows examples of possible responses.

To ensure that the participants understand the rules before attempting the experimental session there are two, 20-minute, pretraining blocks, one for each stimulus type (faces/buildings and shapes/lines). The experimental sessions comprised of two, 20 minute test blocks, one for each stimulus type. All participants perform the task with faces/buidings and then with shapes/lines, with a short break between the two blocks if they wish.

Figure 1.8. Examples of responses from the task with the faces/buildings (left panel) and shapes/lines (right panel) as the stimuli.



1.3.5 The go/no-go task (CANTAB)

A general purpose of the go/no-go test is to measure the decision making abilities and inhibitory control of responses. The clinical measure provided by the task would be whether individual is able to withhold the response whereas it is necessary. Usually, during the go/no-go test a participant is required to perform a particular action when a certain set of stimuli is presented or inhibit that action under a different set of stimuli: to press button – go, not to press button – no-go. Further, there is a number of variants of this test, including the CANTAB version and the Mindstreams version.

In one version the test consists of a number of blocks. Each block contains a series of words which can be subdivided into three affective categories: neutral, negative and positive. The participant is supposed to press button every time when the appeared stimulus matches the given category.

The Mindstreams version of the go/no-go test is a variation of the Continuous performance task that examines executive function and attention (Riccio *et al.*, 2001). In this version of the task participants are presented with a string of English letters. They are asked to respond immediately after the presentation of any letter except 'X'.

In the other version of the go/no-go task participants are presented with a large coloured squares at variable delays. According to the test design, each square can be of four colours. The instruction requires from participants to press a mouse button only in those cases when the presented square is of any colour except red. The response (pressing button) must be as quick as possible.

There is an 'expanded' version of the go/no-go test that includes additional levels of difficulty. Some of these levels are created by increasing the

proportion of red squares, by creating a distraction using additional shapes in the periphery, or by reducing the inter-stimulus interval. By these ways, the expanded version of the go/no-go test challenges executive function and attention and allows accomplishing a more detailed performance profiling.

The go/-no-go test allows the analysis of response inhibition and response time. In some versions the errors made by participants could be classified as omission and commission errors whereas omission errors might reflect impaired sustained attention, while commission errors could reflect such underlying processes as impulsivity and a deficit in memory and attention (Halperin *et al.,* 1991). The go/no-go test might help to discriminate different clinical groups, including individuals with attention-deficit-hyperactivity disorder and head injuries from healthy population (Burg *et al.,* 1995; Holmes *et al.,* 2002; Ossmann and Mulligan, 2003). Overall, the outcome parameters of the go/no-go test include response time, accuracy and a composite score equivalent of accuracy divided by response time, the number of omission errors, the number of commission errors and the response time associated with commission errors.

The previous studies demonstrated the relevance of the go/no-go task to the orbitofrontal area of the brain. Brutkowski and colleagues (1963) reported that the orbitofrontal lesions in monkeys were found to be associated with deficit in inhibitory control on no-go trials. Furthermore, evidence from animal lesion studies may suggest that only lesions of the lateral but not medial orbitofrontal cortex were accompanied by this deficit (Iversen and Mishkin, 1970; Butters *et al.,* 1973). However, human lesion studies provide evidence that damage in prefrontal area will cause inhibitory control deficit during no-go trials (Black *et al.,* 2000; Slavchesky *et al.,* 2004). Moreover, they show that it was more likely that ventrolateral and dorsomedial parts of the prefrontal cortex rather than orbitofrontal area were involved in the go/no-go task (Aron and Poldrack, 2005).

1.3.6 Decision-making (gambling) tasks

The gambling tasks were designed exclusively for human studies. The most widely used is the Iowa Gambling Task (Bechara *et al.,* 2002). During this task four decks of cards (A, B, C, and D) are presented and participants are required to make a choice between them. Every choice made by individual results in the payout of money. The choice of decks A and B leads to the payout of a large amount of money or a large loss, while the choice of decks C and D results in a small payout of money or a small loss. This task is designed in a such a way that consistent choice of decks C and D will result in a gain of money while persistent choice of decks A and B will lead to an eventual loss of money (the reward and punishment contingencies). The instructions to participants are to gain as much money as they can but no explanations are provided about the reward and punishment contingencies. However, subjects are warned that some of the decks are better than the others. In order to succeed in this task participants have to estimate each deck based on their gaining experience and develop the correct strategy. It is believed that this task tests the ability of making real - life decisions.

The alternative to the Iowa Gambling Task is the Cambridge Gambling Test (Rogers *et al.,* 1999). Unlike in the Iowa Gambling Task, the Cambridge Gambling Test provides probabilities on each trial instead of including learning elements. During this task a number of coloured (blue and red) squares is presented and participants are required to identify the location of the token (under the blue or under the red square) in every given trial. The number of the blue or red squares that appeared during the trial reflects probabilities. The instructions are to estimate those probabilities and then to decide how much participants are prepared to bet that their estimation is correct.

The reported findings may suggest that gambling tasks could be associated with the frontal lobe areas. However, these results are inconsistent. While some of them reported the association of probabilistic judgement with the orbitofrontal cortex (Rogers *et al.,* 1999), other studies suggest the sensitivity of the right ventromedial prefrontal cortex to the decision making (Bechara *et al.,* 1998; Tranel *et al.,* 2002). Furthermore, Fellows and Farah (2005) discussed the possibility that the reversal learning element of the Iowa Gambling Task rather than decision making might associate this task with damage of the ventromedial prefrontal cortex.

1.3.7 Social processing and theory of mind

Theory of mind is related to the ability to understand knowledge, intentions and beliefs of others. There are different versions of the theory of mind, including the 'false belief' tasks such as 'Sally - Anne' and 'Smarties'. In these tasks participants with autism regardless of age and children below the age of four or so experience difficulties with conceiving an idea of the other person creating a representation of the reality which varies from their own representation of the world.

An ability to create a representation of representation (or meta-representation) usually develops in children of about the age of two. At this period children normally demonstrate a new ability to pretend playing (Leslie, 1987). Such mental representations develop, if the development is normal, into the ability to understand mental states, intentions and feelings of others. Around age of four children become normally able to be successful in false belief tasks. Baron - Cohen and colleagues (1994) subdivide this ability into understanding of the first and second order beliefs. He named a first order belief that child might attribute to another person. A second order belief is the child's realization that another person might have beliefs about some third person. The understanding of the first and second order beliefs develops at a

different age. Baron - Cohen (1995) reported that none of his autistic children could perform test successfully on second order beliefs.

Evidence from multiple neuroimaging and electrophysiological studies associated impairment in the theory of mind with the frontal lobe dysfunction (Leslie, 1991; Stuss *et al.,* 2001 a; Gregory *et al.,* 2002; Gallagher and Frith, 2003; Lough *et al.,* 2006).

1.4 Conclusion

The orbitofrontal cortex is a large multifunctional area that is widely interconnected with many areas of the brain including the amygdala, insula, and cingulate cortex. The pathway between the orbitofrontal cortex and striatum may control dopaminergic substantia nigra pars compacta neurons and therefore influence behaviour. Moreover, given that the cholinergic innervation of orbitofrontal cortex arrives from the nucleus basalis of Meynert, and the orbitofrontal cortex projects into the nucleus basalis, it is possible that the OFC may control cholinergic input to the entire cerebral cortex. Further, sulcogyral morphological variants were found altered in patients with schizophrenia. This suggests that the orbitofrontal cortex might be the most important area in the search for markers to predict development of mental illnesses.

Chapter 2

Neuroimaging of orbitofrontal cortex in patients with schizophrenia and bipolar disorder and their unaffected relatives

This chapter, firstly, reviews the literature concerning the aetiology and pathogenesis of schizophrenia and bipolar disorder. Secondly, the chapter contains a summary of the structural and functional neuroimaging findings related to the orbitofrontal cortex in patients with schizophrenia and bipolar disorder and in those at high genetic risk of developing schizophrenia or bipolar disorder due to familiar vulnerability. Thirdly, connectivity findings associated with two disorders are discussed as these may provide a reasonable explanation of the structural and functional MRI findings. Lastly, the chapter describes two small projects that were conducted during this PhD which contribute to the content of this chapter and the thesis as a whole.

2.1 Introduction into schizophrenia and bipolar disorder

According to the national official statistics report of the World Health Organization (2001) one in four of the general population will be affected by a psychiatric disorder. This indicates that approximately 15 millions in the UK will suffer from mental health problems and more will experience the difficulties of caring for someone with a mental illness. Bipolar affective disorder and schizophrenia are the most common debilitating mental illnesses among psychiatric disorders in the UK. Given that the present study is dedicated to investigating of the orbitofrontal cortex in schizophrenia and bipolar affective disorder, this chapter will be mostly committed to the reviewing and comparing of these two major psychiatric illnesses.

2.1.1 Schizophrenia

Schizophrenia is a debilitating illness. It is a heritable psychiatric disorder clinically characterized by positive and negative symptoms including impairment in the perception or expression of reality manifesting as hallucinations, delusions, disorganized speech and thinking and significant occupational or social dysfunction. It was previously described by Kraepelin over a hundred years ago as 'Dementia Praecox' (Kraepelin, 1986) and was portrayed as a perceived functional deterioration over time with young age of onset. Later, Bleuer used the term 'schizophrenia' to describe disintegration between different cognitive processes in 'Dementia Praecox' as a central feature of the disorder (Bleuer, 1911). Then, Schneider (1959) referred to specific type of delusions (abnormal beliefs) and hallucinations (abnormal perceptions) as 'first-rank' symptoms of schizophrenia, said to be pathognomic of the condition in the absence of overt brain disease.

Modern psychiatric classifications such as the Diagnostic and Statistical Manual of the American Psychiatric Association version IV (DSM-IV)

(American Psychiatric Association, 1994) and the International Classification of Diseases version 10 (ICD-10) refer to positive and negative symptoms when describing schizophrenia (See **Figure 2.1**). The positive symptoms are used to describe behavioural and perceptional excesses and include delusions, hallucinations, disorganised speech and behavioural abnormalities. The negative symptoms symbolize loss of normal function (Strauss *et al.,* 1974) and consist of alogia (abnormalities of the flow of language and thought), avolition (reduced motivation to initiate goal - directed behaviour), affective blunting (abnormalities in expression of emotions), and anhedonia (reduced ability to experience pleasure). The above symptoms can vary among patients and lead to cognitive deficits that could be characterized by a general reduction of IQ (Johnstone, 1991; Johnstone *et al.,* 2000), deficit in attention, memory, executive functions and language (Goldberg, 2003; Goldberg and Barr, 2003; Goldberg *et al.,* 2003).

Figure 2.1. Diagnostic criteria for schizophrenia.

DSM-IV	**ICD-10**
Duration	
One month of characteristic symptoms	More than one month
Six month of social-occupational dysfunction	
Characteristic symptoms	
At least one of	
Bizarre delusion	Thought echo, thought insertion or withdrawal or broadcast
Third person auditory hallucination	Passively delusional perception
Running commentary	Third person auditory hallucination, running commentary
	Persistent bizarre delusions
Or two or more of	
Hallucinations	Persistent hallucinations
Disorganised speech	Thought disorder
Delusions	Catatonic behaviour
Negative symptoms	Negative symptoms
Grossly disorganised behaviour	Significant behaviour change
Exclusion criteria	
Schizoaffective or mood disorder	Mood disorder, schizoaffective disorder
Direct consequence of substance abuse or general medical condition	Overt brain disease
Pervasive developmental disorder	Drug intoxication or withdrawal

The typical age of onset of schizophrenia is in adolescence or early adulthood. There is a gender effect on the age of onset, whereas in men schizophrenia develops usually between 20 and 24 years, while in women this peak is less prominent and followed by a second peak around the age of 35 years (Hafner *et al.,* 1993; Jablensky, 2003).

According one of the prevailing pathogenic model, schizophrenia is described as a neurodevelopmental illness that leads to abnormal synaptic connectivity. Evidence suggests an involvement of domaninergic (overstimulation of the D_2 receptors in striatum and understimulation of the D_1 receptors in prefrontal cortex) and glutamatergic (involving prefrontal N-methyl-d-aspartate (NMDA) receptors) systems in the development of schizophrenia (Laruelle *et al.,* 2003; Coyle, 2006).

2.1.2 Bipolar affective disorder

According to the report of the World Health Organization bipolar affective disorder remains the sixth leading cause of disability in the world. This illness represents an increasing economic, social and health problem in the future (Murray and Lopez, 1996, 1997). Bipolar affective disorder is well known as a heritable psychiatric illness that is characterised by unstable mood and disrupted behaviour. Those affected could develop either manic or depressive episodes interspersed with periods of remission. During manic or hypomanic (less severe manic) episodes, patients experience decreased sleep, increased drive and grandiose affect. The illness may culminate in psychosis. The Diagnostic and Statistical Manual of Mental Disorders (DSM) developed by the American Psychiatric Association distinguishes bipolar I disorder (experience of full manic episodes interspersed with episodes of major depression) and bipolar II disorder (combination of hypomanic and depressive episodes). According to ICD-10 bipolar affective disorder is defined as a mental illness with repeated episodes (there must be at least

two of them) of disturbed mood and behaviour. During mania or hypomania this disturbance would consist of increased energy and activity and an elevated mood. During depression there will be decreased energy and activity and a lowering mood.

A number of studies reported an association between bipolar affective disorder and other mental illnesses including alcoholism and substance misuse (Regier *et al.,* 1990). There was an expected life span reduction observed of 9.2 years. Moreover, one in five patients with bipolar affective disorder might commit suicide. The annual National Health Service (NHS) cost of the bipolar disorder management was estimated to be 199 million pounds. 35% of this cut is estimated to be accounted for by the cut of inpatient care (Das Gupta and Guest, 2002). This cost is increasing as Young and colleagues (2011) reported the estimated annual NHS cost of bipolar disorder for the period 2009/2010 to be £342,000,000.00 which is larger than the cost estimated 10 years ago by Das Gupta and Guest (2002).

The actual cause of bipolar affective disorder is not fully known, however, evidence from inheritance studies suggests that this illness runs in families. Although bipolar disorder might occur at any age, commonly, this illness develops between 18 and 24 years of age. Both men and women are vulnerable and individuals from any background can develop schizophrenia or bipolar affective disorder. According to different pathogenic theories dysfunction of serotonin and norepinephrine systems is involved in the development of bipolar disorder (Young *et al.,* 1994). There is also the cholinergic - aminergic balance hypothesis suggested by Janowsky and colleagues (Newberg *et al.,* 2008). According to this theory an increased ratio of cholinergic to adrenergic activity might be associated to the pathophysiology of depression. When this ratio is decreased manic episode might develop. Another hypothesis suggests that low serotoninergic functioning might result in the development of both manic and depressive

episodes through causing defective dampening of other neurotransmitters (Bortolato *et al.,* 2013). The evidence from behavioural, post - mortem and neuroimaging studies highlighted some mechanisms that might be involved in the pathophysiology of the bipolar disorder. Neurobiological models of this illness were based on the brain areas involved in integrating emotions considering their instability as a core feature (Phillips *et al.,* 2003; Strakowski *et al.,* 2005).

2.1.3 Bipolar disorder versus schizophrenia

There is an ongoing debate featuring commonalities and differences between bipolar disorder and schizophrenia. Despite some distinguishing clinical characteristics there are indications of considerable overlap in symptoms in patients with these conditions (Siris, 2000; Keck *et al.,* 2003; Murray *et al.,* 2004; Kempf *et al.,* 2005; Bora *et al.,* 2008). Common neurocognitive deficits in patients with bipolar disorder or schizophrenia have been found in several areas including executive function. However, this impairment was found less evident in those with bipolar affective disorder compared to patients with schizophrenia (Krabbendam *et al.,* 2005; Bora *et al.,* 2008). Similarly, some research groups reported that patients with schizophrenia and bipolar disorder shared many brain structural and functional abnormalities, including in prefrontal regions (Lawrie and Abukmeil, 1998; Shenton *et al.,* 2001; Phillips *et al.,* 2003; Strakowski *et al.,* 2005; Glahn *et al.,* 2008; Arnone *et al.,* 2009).

Nevertheless, a number of studies discovered clear differences between schizophrenia and bipolar affective disorder despite some similar clinical symptoms in patients (Harrow *et al.,* 2000; Depp *et al.,* 2007; Gruber *et al.,* 2008; McIntosh *et al.,* 2008; Ringen *et al.,* 2008; Tabarés - Seisdedos *et al.,* 2008; Brambilla *et al.,* 2011).

One of the studies (the paper is prepared for submission) was related to examining impairment in attentional set - shifting in patients with bipolar affective disorder and schizophrenia. The nature of this deficit was investigated through the search strategy that participants employed while trying to identify the target element from a pair of multidimensional stimuli. The task that was used is described in details in **Chapter 1** of this thesis (See the subtitle '**1.3.4 Event-related fMRI task (Cambridge)'** of the **Chapter 1** for more detailed description of this task). The recruited control individuals, patients with schizophrenia and bipolar disorder were age - matched. The search strategy of each participant was possible to identify due to partial feedback that was delivered after every second choice. The results of this study were important as they allowed distinguishing the patient group performance based on the differences in the search strategies employed by patients and healthy individuals. Although both schizophrenia and bipolar disorder patient groups differed from healthy volunteers identifying fewer targets and making more errors, the types of errors show a divergence between patients with schizophrenia and patients with bipolar affective disorder, distinguishing further these two major mental illnesses. While patients with schizophrenia were making more perseverative errors, repeatedly choosing the same stimulus following negative feedback, patients with bipolar affective disorder were more likely to make non - perseverative errors following positive feedback. Patients with bipolar affective disorder and healthy controls did not differ from each other in the number of perseverative responses.

Despite all the published knowledge on the pathogenesis, genetic associations and structural and functional brain abnormalities in these serious psychiatric conditions there are no techniques or known markers that allow us to predict their development in high risk populations. Thus, preventive measures and treatment can be only initiated when the disorder has developed. This creates a problem as episodes of either bipolar disorder

or schizophrenia are traumatic for patients and their relatives (Morrison *et al.,* 2003), and every episode may cause an increasing, sometimes irreversible, cognitive impairment (Joyce *et al.,* 2005). This thesis will demonstrate that a combination of the orbitofrontal sulcogyral patterns with other brain structures (such as paracingulate gyrus; although, there could be other markers as well, including genes) might improve prediction of those from the high risk population who will or will not develop schizophrenia or bipolar affective disorder. If successful, such predictive systems could provide an opportunity for earlier and, possibly, preventive treatments that will definitely improve future opportunities and quality of life of those at high risk of developing schizophrenia or bipolar affective disorder.

2.2 Genes associated with schizophrenia and bipolar disorder

Evidence suggests that both schizophrenia and bipolar affective disorder are multifactorial diseases characterised by multiple genetic susceptibility (Gottesman and Shields, 1976; Kessler, 1980; Tsuang *et al.,* 1991; Mitchell *et al.,* 2010). In case of schizophrenia, 1% of the world - wide population has a lifetime risk of developing the illness and this is increased to 9 - 13% among first - degree relatives (Gottesman, 1991). Each genetic component contributes on its own or in combination with the other elements to a degree of risk. A number of genes were identified in recent association studies that suggested vulnerability to schizophrenia and/or bipolar disorder. Some of those genes were found to be involved in neurotransmitter and signalling pathways that were previously found to be implicated in schizophrenia and bipolar disorder (Kato, 2007). For example, several genes, including DGKH, NXH, A2BP1, Dfnb31, PDLIM5 and IMPA-2 (See **Figure 2.2**), have been identified as risk genes of developing schizophrenia or bipolar disorder and are known to interact with the PKC and GSK-3β (Baum *et al.,* 2008). Risk genes including GRM3 and 4, DAO, GRIN2B and G72/DAOA are known to function within glutamate signalling pathways (Kato, 2007). Receptors genes

for dopamine, GABA and serotonin (Kato, 2007), could also be identified there.

Evidence from genome wide linkage studies associated schizophrenia with several loci, including 5q, 3p, 11q, 6p, 1q, 22q, 8p, 20q and 14p (Lewis *et al.,* 2003). Moreover, schizophrenia was found to be related to Catechol O - Methyltransferase Val allele (Glatt *et al.,* 2003 a), the dopamine receptors D2 (Glatt *et al.,* 2003 b), D3 (Jönsson *et al.,* 2003 a; Shaikh *et al.,* 1996) and D4 (Jönsson *et al.,* 2003 b), Neuroregulin, D - Amino Acid Oxidase and Dysbindin (Jönsson *et al.,* 1997).

Bipolar disorder was found to be associated with 18p11.2, 21q22, 22q11 - 13, 18q22, 12q24 and 4p15 (Berrettini, 2002).

Figure 2.2. Genes that were found to be involved in pathophysiology of schizophrenia and bipolar affective disorder.

Gene	Name	Location	Function	References for schizophrenia	References for bipolar disorder
NRG1	Neuregulin 1	8p12-p21	Broad involvement in neuronal development, survival and synaptic function	Stefansson *et al.,* 2002; Corfas *et al.,* 2004; Addington *et al.,* 2007; Blackwood *et al.,* 2007; Mechelli *et al.,* 2008	Blackwood *et al.,* 2007; Mechelli *et al.,* 2008
DTNBP 1	Dysbindin	6p22	Member of dystrophin protein complex and biogenesis of lysosome-related organelle complex; potential presynaptic effects on glutamate release at excitatory synapses	Straub *et al.,* 2002; Numakawa *et al.,* 2004; Narr *et al.,* 2009; Fallgatter et al., 2010	Raybould et al., 2005; Joo *et al.,* 2007
G72 (DAOA)	D-aminoacid oxidase activator	13q22-34	Potential activator DAAO; indirect effects on glutamate-mediated signaling	Chumakov *et al.,* 2002; Opgen-Rhein *et al.,* 2008; Shi *et al.,* 2008; Ma *et al.,* 2009	Backlund *et al.,* 2008; Shi *et al.,* 2008; Grigoroiu-Serbanescu *et al.,* 2010
DAAO	D-aminoacid oxidase	12q24	Metabolises D-serine, an endogenous modulator of the NMDA	Chumakov *et al.,* 2002; Tsai and Coyle, 2002; Liu *et al.,* 2004; Madeira *et al.,* 2008;	Papagni *et al.,* 2011

			receptor	Papagni *et al.,* 2011	
RGS4	The regulator of G-protein signaling-4	1q21-23	GTPase activator that modulates signal transduction through dopamine, metabotropic glutamate and muscarinic receptors (Larminie *et al.,* 2004; Ross and Wilkie, 2000)	Chowdari *et al.,* 2002; Guo, *et al.,* 2006; Ding and Hegde, 2009	Huuhka *et al.,* 2008; Ding and Hegde, 2009
COMT	Catechol-O-methyl-transferase	22q11	Metabolism of dopamine; regulation of extracellular dopamine levels in prefrontal cortex	Egan *et al.,* 2001; Shifman *et al.,* 2002; Paterlini *et al.,* 2005; Prata *et al.,* 2009; Pomarol–Clotet *et al.,* 2010	Benedetti *et al.,* 2010, 2011; Virit *et al.,* 2011; Soeiro-de-Souza *et al.,* 2012 a; Hatzimanolis *et al.,* 2013
DISC1	Disrupted-in-schizophrenia 1	1q42.1	Multifunctional; possible involvement in cytoskeletal and centromere function and in cell membrane receptor localization and signal transduction	Hennah *et al.,* 2003; Hodgkinson *et al.,* 2004; Burdick *et al.,* 2005; Callicott *et al.,* 2005; Cannon *et al.,* 2005; Kamiya *et al.,* 2005; Millar *et al.,* 2005; Thomson *et al.,* 2005; Lipska *et al.,* 2006; Blackwood *et al.,* 2007; DeRosse *et al.,* 2007; Mackie *et al.,* 2007; Szeszko *et al.,* 2008; Takahashi *et al.,* 2009; Tomppo *et al.,* 2009 a; Nicodemus *et al.,* 2010;	Hodgkinson *et al.,* 2004; Maeda *et al.,* 2006; Blackwood *et al.,* 2007; Prata *et al.,* 2011; Schosser *et al.,* 2010; Song *et al.,* 2010; Chakirova *et al.,* 2011

				Chakirova *et al.,* 2011; Prata *et al.,* 2011	
BDNF	Brain-derived neurotrophic factor	11p13 - 14	Important in synaptic plasticity and in the survival and function of midbrain dopamine neurons (striatum, including neurons in the ventral tegmental area (VTA), the nucleus accumbens); modulates NMDA receptor properties, affects hippocampal function (Egan *et al.,* 2003)	Kawashima *et al.,* 2009; Jindal *et al.,* 2010; Spalletta *et al.,* 2010; Zhang *et al.,* 2013	Tang *et al.,*2008; De Aguiar Ferreira *et al.,* 2010; Fernandes *et al.,* 2011;Soeiro-de-Souza *et al.,* 2012 b

Reports from some of genetic studies demonstrated increasing evidence for an overlap in genetic susceptibility for bipolar affective disorder and schizophrenia. However, evidence from other studies is somewhat controversial. Although genes that were found to be associated with schizophrenia and bipolar disorder may be the same (such as DISC1, G72, DAO, NRG1, GRM3, GRM4 and GRIN2B; Kato, 2007), the distribution of pathological alleles and the variants of these genes in patients with schizophrenia or bipolar disorder could be different (Hashimoto *et al.,* 2006; Palo *et al.,* 2007).

Chakirova and colleagues (2011; See **Appendix I** of this thesis) conducted a study analysing three risk variants (rs1538979, rs821577, and rs821633) in the Disrupted – in – Schizophrenia - 1 (DISC1) gene that have previously been associated with both schizophrenia and bipolar disorder (Hennah *et al.,* 2009). This study examined the effects of the DISC1 risk variants on brain function using functional Magnetic Resonance Imaging (fMRI). Thirty three healthy volunteers, twenty patients with schizophrenia and thirty six patients with bipolar affective disorder were scanned while performing the Hayling Sentence Completion Task (HSCT, see detailed description of this task in **Chapter 4** of this thesis). The importance of the results in this study is that it demonstrates differences between patients with schizophrenia and patients with bipolar affective disorder while showing the effects of risk alleles on brain function within healthy controls. For example, in the healthy individuals carrying of the risk associated allele of SNPs rs1538979 and rs821633 resulted in the decreasing of brain activation of the cuneus. Further, there was an effect of SNP rs1538979 found in the pre/postcentral gyrus with decreased activation of this area in healthy controls and increased activation in patients with schizophrenia. Moreover, in the bipolar disorder group there was decreased activation found in the risk carriers of SNP rs821633 in the inferior parietal lobule and left cingulate cortex. Clusters in the precentral gyrus, left middle temporal gyrus and left cerebellum were found to be

significant on examining the group×genotype interactions. These findings provide with an important example of genetic impact (DISC1 variants in this case) on brain function and suggest genetic component to a model that may predict development of schizophrenia or bipolar disorder in the high risk population. If the pathophysiology and pathogenesis of schizophrenia and bipolar disorder are to be understood, then identifying the associated genes is essential and this has the potential for informing on the development of more effective treatments. A new and developing research field of elucidating the associations between genes and anatomical patterns on the brain surface may offer a better understanding and even assist in the prediction of the development of schizophrenia and bipolar disorder.

2.2.1 Genes and orbitofrontal cortex

There is a limited amount of studies to date that elucidate genetic associations with the orbitofrontal cortex. Cerasa and colleagues (2011) reported an impact of rs2619539, rs3213207 and rs2619538 of the dystrobrevin - binding protein 1 (DTNBP1 or dysbindin) gene on the cortical thickness of the right medial orbitofrontal cortex in healthy participants. This gene is widely distributed in the human brain, plays an important role in glutamatergic neurotransmission and has been previously associated with schizophrenia (Numakawa *et al.,* 2004; Williams *et al.,* 2004, 2005; Talbot *et al.,* 2006).

2.3 Postmortem studies

The purpose of postmortem studies of schizophrenia and bipolar disorder was to try to identify possible lesions or histological abnormalities that might provide with further insight into the pathophysiology of patients with those major mental illnesses. As this thesis is primarily dedicated to the

orbitofrontal cortex this review is concentrated on the neuropathological findings in the frontal lobe.

Evidence emerging from the postmortem studies suggests abnormalities in neuronal morphology of frontal neurones in patients with schizophrenia. There was a reduction found in neuronal size (Benes and Bird, 1987; Rajkowska *et al.,* 1999) and in neuronal density in layers II, III and IV of the patients' cortex (Benes *et al.,* 1986; 1991; 1993). Moreover, Brodmann's areas 4, 10, and 24 are between the most consistently implicated brain regions.

Postmortem studies of patients with bipolar disorder reported that the anterior cingulate area and orbitofrontal cortex were found to be primarily implicated in this illness (Rajkowska, 2000; Drevets, 2001; Uranova *et al.,* 2001; Cotter *et al.,* 2005; Torrey *et al.,* 2005). This is an important finding for our study considering that the orbitofrontal sulcogyral patterns in connection with the anterior cingulate region improve predictive value of the mental illness development in high risk population (See **Chapters 3**, **4** and **5**). Reductions in volume and/or glial density were discovered in BA 9 (Rajkowska *et al.,* 1999; Cotter *et al.,* 2002) and BA 24 (Ongur *et al.,* 1998; Benes *et al.,* 2000; 2001; Bouras *et al.,* 2001). Rajkowska and colleagues (1999) discovered reduction in cortical thickness, neuronal and glial densities, and neuronal sizes in the orbitofrontal area in patients with major depressive disorder. Specifically, abnormalities were observed in the rostral part of the orbitofrontal cortex in upper cortical layers II – IV, where there was an increase in density of small neurons with proportional decrease in large neuron density, suggesting developmental abnormalities or neuronal atrophy. Molecular studies reported reduction in growth associated protein (GAP - 43), dendritic microtubule associated protein and synaptophysin in the BA 24 (rostral, pre-genual part) implying synaptic pathology in this region (Bouras *et al.,* 2001; Eastwood and Harrison, 2001). McNamara and colleagues (2008)

reported deficit in the orbitofrontal omega - 3 fatty acid docosahexaenoic acid (DHA, 22:6n-3; Brodmann area 10) in the postmortem cortical membranes (this plays an important role in cellular signalling events in brain) as well as impaired arachidonic acid composition and elevation in arachidonic acid metabolism when patients with bipolar disorder are compared to healthy controls adding to a growing body of evidence implicating the orbitofrontal cortex and the omega - 3 fatty acid deficiency in the aetiology and pathophysiology of bipolar disorder.

2.4 Schizophrenia, bipolar disorder and the orbitofrontal cortex: structural and fMRI studies, differences and similarities

Magnetic resonance imaging (MRI) is a method that was developed in the 1970s from principles discovered and described by chemists in the 1940s (Purcell *et al.,* 1946). A large amount of neuroimaging research identified several changes in the brain structure of those affected by bipolar disorder or schizophrenia, although, these findings diverge across studies.

2.4.1 Structural neuroimaging in schizophrenia and bipolar disorder and in their unaffected relatives

A number of studies examined brain structure abnormalities in patients with bipolar disorder and schizophrenia (Johnstone *et al.,* 2005; Owens and Johnstone, 2006; Gruber *et al.,* 2008; McIntosh *et al.,* 2008). From these studies various findings in frontal lobe region emerged. There was a prefrontal cortex volume reduction found in patients with schizophrenia when they were compared to controls (Harvey *et al.,* 1993; Andreasen *et al.,* 1994; Bilder *et al.,* 1994; Gur *et al.,* 2000). Specifically, reduction of volume in areas including anterior cingulate and orbitofrontal regions were discovered using parcellation method (Crespo-Facorro *et al.,* 1999; Goldstein *et al.,* 1999; Gur *et al.,* 2000), deformation based morphometry technique (DBM, Gaser *et al.,*

1999) and voxel based morphometry method (VBM, Chua *et al.,* 1997; Wright *et al.,* 1999).

There were much less structural abnormality found in the frontal region in patients with bipolar disorder using structural magnetic resonance imaging, and the findings were controversial and less conclusive. There was a grey matter reduction found in the left middle and superior frontal gyri and in the right inferior and middle frontal gyri in individuals with bipolar affective disorder when compared to healthy controls (Lopéz - Larson, 2002). However, Kubicki and colleagues did not discover any differences between bipolar patients and healthy controls in the frontal cortex using VBM method (Kubicki *et al.,* 2002). Lacerda and colleagues (2004) reported that unmedicated patients with major depressive disorder had reduced grey matter volume in the left lateral and right medial orbitofrontal cortex compared to controls. Moreover, they discovered that the left lateral orbitofrontal cortex was negatively correlated with age but only in patients with depression. Furthermore, there was a gender effect associated with the OFC in such a way that only male but not female patients with depression had smaller left and right medial orbitofrontal volumes when compared to healthy participants with the same gender (Lacerda *et al.,* 2004). Two more studies (Lai *et al.,* 2000; Bremner *et al.,* 2002) discovered bilateral reduction of the orbitofrontal cortex in patients with depression when compared to healthy volunteers. There was also increased lesion density found in the medial orbitofrontal cortex white matter in elderly patients with major depressive disorder (MacFall *et al.,* 2001).

Individuals at high risk of developing schizophrenia also appeared to have some structural abnormalities in frontal lobe region. There was a reduction in grey matter density found in the Edinburgh High Risk Study in medial prefrontal cortex using voxel based morphometry technique in high risk subjects compared to healthy controls (Job *et al.,* 2002). Moreover, higher

genetic liability was found to be associated with decreased left and right prefrontal lobe volume within high risk participants (Lawrie *et al.,* 2001).

There was a number of structural abnormalities reported in unaffected relatives of patients with bipolar disorder that were similar to those found in patients with bipolar disorder (McIntosh *et al.,* 2004; McIntosh *et al.,* 2005; McDonald *et al.,* 2006; McIntosh *et al.,* 2006; Frazier *et al.,* 2007; Hajek *et al.,* 2009; Chaddock *et al.,* 2009).

2.4.2 Functional Magnetic Resonance Imaging

Functional Magnetic Resonance Imaging (fMRI) is a functional Neuroimaging technique that is uses the measurement of the blood oxygenation level (BOLD – the blood oxygenation level-dependent contrast) to examine brain function (Ogawa *et al.,* 1990). Functional magnetic resonance imaging is based on differences in the magnetic susceptibility between oxygenated arterial blood and fully deoxygenated venous blood (Pauling and Coryell, 1936). During fMRI scanning procedure, the brains of the participants are scanned repeatedly usually using the fast imaging technique known as echo - planar imaging (EPI; Mansfield, 1977), while subjects perform some cognitive task containing periods of activity and rest. The rest period is used as a baseline for further statistical analysis. During the active period of the fMRI task, the areas of the brain that involved in the task normally produce an increased MRI signal as blood flow to the active brain regions will be increased. In order to reveal those regions the MRI scans will need to undergo a number of pre-processing steps including registration of the images, head movement correction that might occur during the experiment, and smoothing the data that helps to improve the signal to noise ratio. The following statistical analysis helps to detect the pixels in the MRI scan that demonstrates a response to the stimulus.

2.4.3 fMRI artefacts

It is important to note that magnetic resonance images suffer from a number of artefacts especially in the orbitofrontal area. These artefacts include subject movements during the scan, cardiac and respiratory gating, truncation artefact due to the limited number of used sampling points (results from application of a Fourier transformation to creating the image from raw data; observed as 'ringing' – dark or light lines parallel to the edge of the image), signal loss in the orbitofrontal area due to inhomogeneity of the magnetic field and susceptibility artefacts. 'Susceptibility artefacts' were reported in connection to the inferior part of the frontal lobe where the air: tissue boundaries (the frontal, sphenoidal, and ethmoidal sinuses) result in signal reductions due to differences in magnetic susceptibility (Ojemann *et al.,* 1997; Lipschutz *et al.,* 2001).

2.4.4 Functional neuroimaging in schizophrenia and bipolar disorder and in their unaffected relatives

Fahim and colleagues (2005) investigated brain activity in patients with schizophrenia with and without 'flat affect'. 'Flat affect' or emotional blunting has been considered as a core symptom of this illness (Bleuler, 1950). Participants viewed a series of emotionally negative and neutral pictures while they were scanned (Fahim *et al.,* 2005). Patients who did not have 'flat affect' showed a greater negative emotional reaction to the viewing of the negative pictures comparing to those patients with 'flat affect'. Interestingly, the ventrolateral orbitofrontal cortex was activated in those patients with schizophrenia who were without 'flat affect' when negative pictures versus neutral were contrasted (Fahim *et al.,* 2005). Brodmann's Area 47/12 (the ventrolateral part of the orbitofrontal cortex) was previously found to be associated to the external and internal induction of the negative emotional states such as anxiety, sadness and anger (Pardo *et al.,* 1993; George *et al.,*

1995; Fredrikson *et al.,* 1997; Beauregard *et al.,* 1998; Dougherty *et al.,* 1999; Kimbrell *et al.,* 1999; Damasio *et al.,* 2000; Levesque *et al.,* 2003; Pelletier *et al.,* 2003). This cortical region receives limbic and sensory inputs from the areas including entorhinal and perirhinal cortex and amygdala (Price, 1999). Therefore, activation of the BA 47/12 in patients with schizophrenia without 'flat affect' might be explained by the integration of the viscerosensory information and changes of the emotional state of the participants (Fahim *et al.,* 2005). Moreover, Willis and colleagues (2010) investigated the ability of patients with the orbitofrontal cortex lesions to judge the approachability of emotional faces. They discovered that patients with orbitofrontal lesions experienced difficulties with the judgment of negative facial expressions when they were compared to healthy individuals and patients with lesions in the frontal lobe excluding the orbitofrontal cortex.

Strikingly, various Brodmann' areas of the orbitofrontal cortex may contribute differently to the processing of emotions. For example, the right BA 47/12 was activated during viewing of the sad film excerpts, while the orbitofrontal BA 11 in the right hemisphere was associated with voluntary suppression of sadness in female healthy volunteers (Levesque *et al.,* 2003). Further, previous studies suggested that the orbitofrontal cortex exerts inhibitory control in order to protect goal-directed behaviour from interference (Roberts and Wallis, 2000). However, the contribution of different Brodmann' areas to the inhibitory control could vary. For example, the Brodmann' area 11 is involved in the voluntary suppression of sadness (Levesque *et al.,* 2003), while BA 9 might be responsible for the inhibitory control in attentional set-shifting (Dias *et al.,* 1996).

Evidence suggests that patients with bipolar disorder might be impaired in variable cognitive functions such as executive function (also this may not be at the same degree as in patients with schizophrenia) and language processing (Arts *et al.,* 2008). Functional imaging studies associated bipolar

disorder with abnormalities in the prefrontal cortex, striatum, and limbic regions, including the amygdala (Strakowski *et al.,* 2005; Phillips and Vieta, 2007; Womer *et al.,* 2009). Importantly, a number of neuroimaging studies reported abnormalities in the orbitofrontal cortex of patients with bipolar affective disorder (Blumberg *et al.,* 1999; Lopez - Larson *et al.,* 2002; Kruger *et al.,* 2003; Altshuler *et al.,* 2005).

In manic states patients develop flight of ideas (may rapidly flit from one topic to another) and copious speech ('pressure of speech'), while during depressive episodes patients' spontaneity and content of speech is diminished. Evidence confirmed that patients with bipolar disorder can have impairment of their performance on verbal fluency tests (Dixon *et al.,* 2004). Further evidence suggests involvement of the prefrontal and lateral temporal regions as well as subcortical structures, including the striatum and medial temporal lobe, in verbal fluency and word generation tasks during functional MRI. Previous studies reported increased activation of the ventral striatum and ventral prefrontal cortex in participants with bipolar affective disorder compared to healthy controls (McIntosh *et al.,* 2008). In this study participants performed a sentence completion paradigm (an extension of the verbal fluency task) under the scanner. There was an association found between the prefrontal (Curtis *et al.,* 2001; Curtis *et al.,* 2007) and cingulate cortex (Curtis *et al.,* 2007; Allin *et al.,* 2010) and language processing in bipolar disorder. The most consistently reported finding was an increased activation of the medial temporal lobe structures especially the amygdala in those with bipolar disorder (Phillips *et al.,* 2008, Cerullo *et al.,* 2009).

A number of studies reported abnormally increased metabolism in the orbitofrontal cortex in unmedicated depressive patients (Cohen *et al.,* 1992; Biver *et al.,* 1994). Moreover, regional cerebral blood flow (rCBF) was changed after treatment with cognitive - behavioural therapy and antidepressants (Brody *et al.,* 1999). Bremner and colleagues observed

relapse into depression that was induced by depletion of tryptophan (Bremner *et al.,* 1997). Similar findings were reported in healthy subjects with induced sadness (Baker *et al.,* 1997) and patients with Parkinson's disease associated with secondary depression (Ring *et al.,* 1994). Moreover, reduced activity in inferior orbitofrontal region was observed in depressed patients with Parkinson's disease when they were compared to healthy individuals and patients with Parkinson's disease without depression (Mayberg *et al.,* 1990). These findings were confirmed by the positron emission tomography study (Liotti *et al.,* 2002). Liotti and colleagues reported decreased activation of the medial orbitofrontal cortex in patients with major depressive disorder after using autobiographic memory scripts for provocation of sadness.

2.4.5 Functional and structural connectivity in schizophrenia and bipolar disorder

Accumulating number of publications suggests shared elements of pathology between schizophrenia and bipolar affective disorder (Fischer and Carpenter, 2009). Existing models of schizophrenia and bipolar affective disorder indicate possible overlap in neuronal network. Strakowski and colleagues (2005) suggested that dysfunction of a prefrontal - subcortical network in combination with a limbic network might be responsible for the affective and psychotic symptoms of bipolar disorder. Abnormalities of the orbitofrontal cortex can mediate such symptoms of depression as impaired social functioning and blunting of emotional affect through its interconnections with the brain areas that are well known to be involved in the pathophysiology of major depressive disorder (Zald and Kim, 2001; Bremner *et al.,* 2002). These brain regions include basal ganglia, amygdala, thalamus, and hippocampus.

2.5 Conclusion

In a summary, although there is some clinical and genetic overlap between bipolar affective disorder and schizophrenia, these illnesses also appear to have differences in pathogenesis, clinical symptoms and genetic variables. Future studies may be able to provide us with better understanding of schizophrenia and bipolar disorder, permit to distinguish them from each other and to predict their development in those at high genetic risk due to familial vulnerability.

Chapter 3

Orbitofrontal sulcogyral patterns in groups of patients with bipolar disorder and schizophrenia and their unaffected relatives

The distribution of the orbitofrontal sulcogyral patterns and anterior cingulate morphology as well as the neuropsychological associations of the orbitofrontal patterns and the associations between the orbitofrontal patterns and paracingulate sulcus in patients with schizophrenia and bipolar disorder and their unaffected relatives were examined. The BrainVISA software automated sulci recognition pipeline was compared to the manual orbitofrontal patterns identification protocol in a search for the ways to make the orbitofrontal sulcogyral pattern identification more accessible.

3.1 Introduction

Given the structure, function, neurotransmitter system and connections within the brain, the orbitofrontal cortex (See **Chapter 1** for details) might be one of the most important areas to look at in the search for a marker which might help to enhance the accuracy of prediction of schizophrenia and bipolar disorder in genetically high - risk families. Schizophrenia and bipolar affective disorder were discussed in details in **Chapter 2**.

A number of studies (See **Chapter 2** for details) reported brain structure abnormalities in patients with bipolar affective disorder and schizophrenia (Johnstone *et al.,* 2005; Owens and Johnstone, 2006; McIntosh *et al,.* 2008; Gruber *et al.,* 2008). Moreover, evidence suggests that acquired damages in the left prefrontal cortex may result in negative symptoms of schizophrenia and in stabilized mood (Pang and Lewis, 1996; See **Chapter 1** for details). Furthermore, Curtis *et al.* (2001) reported a different pattern of frontal responses in patients with bipolar disorder compared to those with schizophrenia. Considering that the orbitofrontal cortex has such an extensive influence through its connections and neurotransmitter systems and is known to be important in emotional processing and executive functioning (Ongur and Price, 2000; Walton et al., 2004; Kringelbach, 2005), it seems reasonable to suggest the involvement of this region in pathophysiology and symptoms of bipolar affective disorder and schizophrenia. Comparing symptomatology of the two major psychiatric illnesses such as social withdrawal, the insidious onset of schizophrenia *versus* more socially appropriate premorbid behaviour and the rapid onset of bipolar disorder (Cannon *et al.,* 1997; Kutcher *et al.,* 1998), and differences in pathogenic theories of the two disorders (association with dysfunction of dopamine and glutamate neurotransmitter systems in the development of schizophrenia compared to the involvement of serotonin and norepinephrine neurotransmitter systems in bipolar disorder), it might be possible to suggest

the OFC as an area with significant potential for distinguishing the two disorders.

Despite the known variability of orbitofrontal sylcogyral morphology, Chiavaras and Petrides (2000) developed a classification by which orbitofrontal sulcogyral patterns could be separated into 3 types based on connectivity of the two main orbital sulci: medial and lateral orbital sulci through the third one - transverse orbital sulcus. They reported the prevalence of type I in a healthy population (identified in 56% of hemispheres) with the minority of two other types: type II was seen in 30% of hemispheres while type III only appeared in 14% of hemispheres.

Later Nakamura and colleagues (2007) announced the alteration of orbitofrontal cortical folding patterns in patients with schizophrenia with increased type III and reduced type I in the right hemisphere. The authors also noticed that possession of type III in patients with schizophrenia was associated with poorer socioeconomic status, more severe psychotic symptoms and more severe cognitive impairment when compared with patients of any other orbitofrontal pattern (Nakamura *et al.,* 2007). Chakirova and colleagues (2010) looked at those at genetically high - risk of developing schizophrenia and established that the orbitofrontal patterning is altered even before schizophrenia is manifested. The authors also enhanced Chiavaras' classification with a rear type IV. Considering alteration of the orbitofrontal patterns in schizophrenia even before the development of this debilitating psychiatric disorder, it seems possible to suggest that orbitofrontal morphology may provide us with novel insight into our understanding of pathophysiology of schizophrenia. Moreover, this raises a question about distribution of orbitofrontal sulcogyral patterns in the other diagnostic groups which till now remains unknown.

This is why an enhanced Chiavaras' classification (identifying types I, II, III and IV) has been applied to subjects with schizophrenia, bipolar disorder and their unaffected relatives. The hypothesis was that the application of this classification system could potentially enable the differentiation of bipolar disorder and schizophrenia from each other on the basis of differences in anatomical structures of the orbitofrontal region and the importance of neurodevelopment in pathophysiology of both disorders. Considering the time - consuming training that is necessary in order to master the manual protocol, the automatic sulci recognition pipeline of the BrainVISA software (http://www.brainvisa.info) was also applied to 20 scans from the present study in the hope of finding an easy future solution.

3.1.1 Distribution of the anterior cingulate morphology

Unlike the distribution of orbitofrontal cortico - folding sulcogyral patterns, the anterior cingulate morphology seems to vary significantly even within healthy population and also in patients with schizophrenia. This could mainly be explained by differences in rating methodology (Leonard *et al.,* 2009).

For example, Fornito and colleagues (2004) reported that the paracingulate sulcus was present in about 30 - 60% of their participants and more prevalent in the left hemisphere. According to Yucel and colleagues (2003) the continuous variant of the cingulate sulcus (one piece) was identified in 87% controls in the left and right hemispheres. Furthermore, there was a gender effect found on the appearance and frequency of the cingulate and paracingulate sulci in the right and left hemispheres (Leonard *et al.,* 2009; Rammetti *et al.,* 2010).

3.1.2 Introduction into classification of orbitofrontal sulcogyral patterns

The first classification of the orbitofrontal sulcogyral patterns was developed and presented by Chiavaras and Petrides (2000). These authors analysed the orbitofrontal sulcogyral patterns in fifty healthy volunteers from the Canadian population. They based their classification on connectivity of the rostral and caudal parts of the lateral and medial orbital sulcus through the transverse orbital sulcus. Although the classification included only three main orbitofrontal sulcogyral patterns, Chiavaras and Petrides (2000) described extensive variability within each type.

3.1.3 Chiavaras' classification

Chiavaras and Petrides described three main orbitofrontal patterns: type I, type II and type III (See **Figure 1.4** in **Chapter 1** of this thesis). The orbitofrontal type I was presented in 56% of hemispheres and was formed by connected rostral and caudal parts of the lateral orbital sulcus via the transverse orbital sulcus, and by the disconnected medial orbital sulcus. The orbitofrontal type II was presented in 30% of healthy hemispheres and was formed by connected rostral and caudal parts of the lateral and medial orbital sulci through the transverse orbital sulcus (the mostly connected orbitofrontal pattern). The orbitofrontal type III was presented in 14% of the healthy hemispheres and is the mostly disconnected type with disjointed rostral and caudal parts of the lateral and medial orbital sulci.

3.1.4 The orbitofrontal type IV

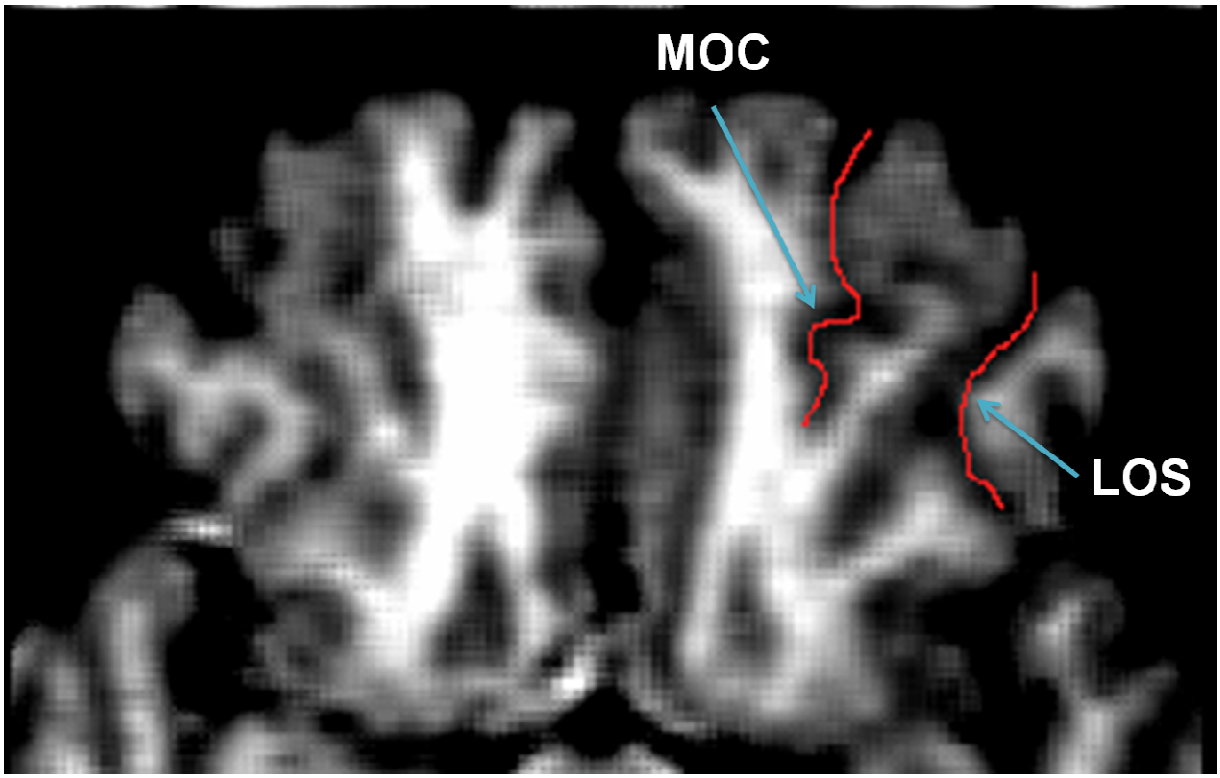
Chakirova and colleagues (2010) reported the presence of the orbitofrontal type IV (See **Figure 1.4** and **Figure 1.5** in **Chapter 1** of this thesis) when the authors analysed one hundred and eighty two brain images including of those at genetic high risk to develop schizophrenia from the Edinburgh High

Risk Study (the EHRS; See **Chapter 4** of this thesis). Given that the number of scans containing this orbitofrontal pattern was comparably small it suggests that this sulcogyral type is rare. This could be a reason why the orbitofrontal type IV was not identified by Chiavaras and Petrides (2000) or Nakamura and colleagues (2007) where the number of scans examined by researchers was relatively smaller. It is important to note that as the numbers of this orbitofrontal sulcogyral pattern in the EHRS were small, it was not possible to analyse the functional importance of this type. Therefore, its role, if there is any, remains unknown.

3.1.5 Absence or disconnection of the transverse orbital sulcus

During present research project the orbitofrontal patterns were analysed in several cohorts that will be described further. There was a small number of scans (in each of three cohorts) which contained the disconnection or even absence of the transverse orbital sulcus (See **Figure 3.1**). As the numbers of hemispheres with disconnected transverse orbital sulcus were even smaller than the numbers of the orbitofrontal sulcogyral type IV in the EHRS, there was not any opportunity to investigate and understand whether there is any underlying meaning of such disconnection.

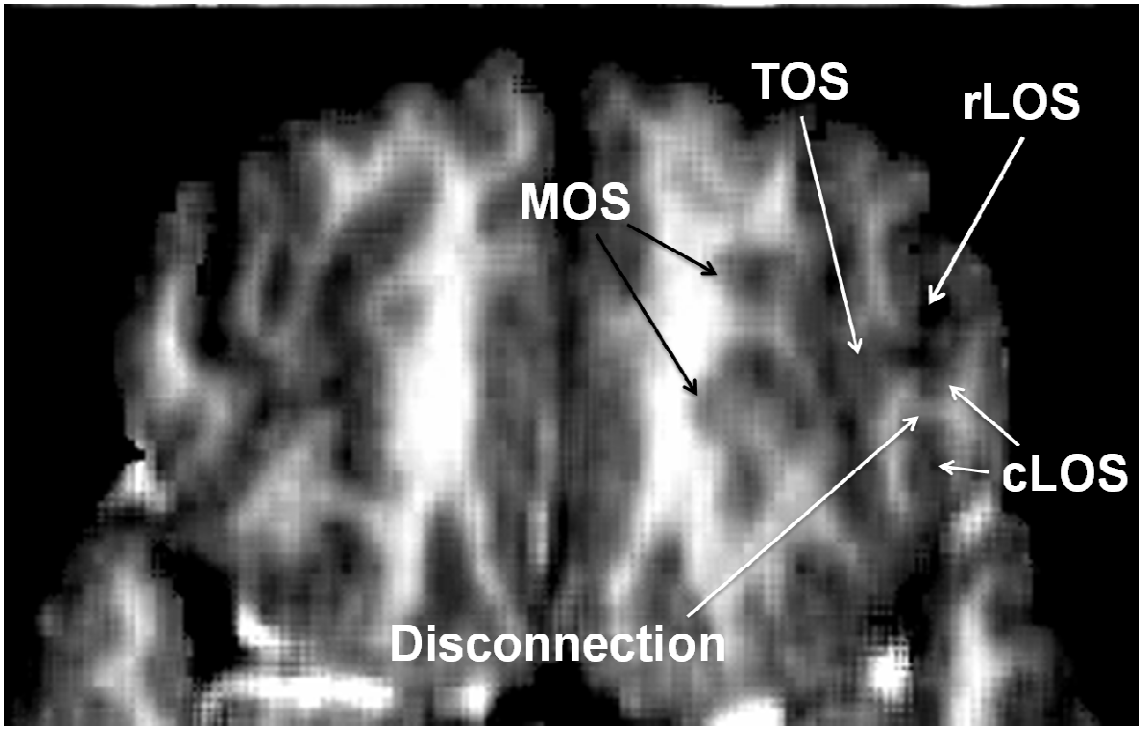
Figure 3.1. This is an example of the disconnected transverse orbital sulcus on the left hemisphere. LOS = lateral orbital sulcus; MOS = medial orbital sulcus. This image was created using MRIcro software.



3.1.6 Disconnected caudal part of the lateral orbital sulcus

There was also made a novel observation that the caudal part of the lateral orbital sulcus might be disconnected (See **Figure 3.2**). Given that this observation was relatively rare there was not any opportunity to analyse the functional significance of this disconnection.

Figure 3.2. Disconnected caudal part of the lateral orbital sulcus on the left hemisphere. rLOS = the rostral part of the lateral orbital sulcus; cLOS = the caudal part of the lateral orbital sulcus; MOS = medial orbital sulcus; TOS = transverse orbital sulcus. This image was created using MRIcro software.



3.1.7 Symmetry - asymmetry in distribution of orbitofrontal sulcogyral patterns

Scans were defined as symmetric when there was the same orbitofrontal pattern identified in the left and right hemispheres: type I in the right and type I in the left hemispheres, type II in the right and type II in the left hemispheres, and type III in the right and type III in the left hemispheres. Those scans, where different orbitofrontal patterns were identified in the right and in the left hemispheres, were classified as asymmetric. Importantly, there were no symmetric scans found with the orbitofrontal type IV. This is a novel

way to examine symmetry of the orbitofrontal morphology and it was not published anywhere before.

3.2 Methodological aspects of sulci identification

3.2.1 Manual sulci recognition protocol

The manual protocol was based on the sulci identification and classification proposed by Chiavaras and Petrides (2000) that suggests a system of three main orbitofrontal patterns (type I, II and III), expanding this Chiavaras' classification with the newly identified type IV (Chakirova *et al.,* 2010; see **Appendix II**). This visual classification entirely depends on the continuity and connectivity of two main orbital sulci (medial and lateral orbital sulci) through the third one – transverse orbital sulcus. In type I the rostral part of the lateral orbital sulcus is connected with the caudal part of the lateral orbital sulcus through the transverse orbital sulcus while the rostral and caudal parts of the medial orbital sulcus are disconnected. Type II, which is commonly described as an 'H - shaped' pattern (Williams *et al.,* 1989), is formed by the union of the lateral, medial and transverse orbital sulci. Type III is characterized by parting of the rostral and caudal portions of both medial and lateral orbital sulci. Type IV is the rarest type and could be identified when the rostral and caudal parts of the medial orbital sulcus are connected while the rostral and caudal parts of the lateral orbital sulcus are disconnected (Chakirova *et al.,* 2010).

The MRIcro software verson 1.40 (http://www.sph.sc.edu/comd/rorden/mricro.html), a free program for viewing medical images, was used to identify orbitofrontal sulci. The transverse, sagittal, coronal slice viewer and 3D render of the MRIcro were involved in the protocol (for more details see Chakirova *et al.,* 2010).

3.2.1.1 Steps of manual sulci identification and typing

The manual protocol of the orbitofrontal pattern identification is described in **Appendix III**.

3.2.1.2 Advantages of manual methodology

Advantages of the manual methodology are:

1. high reliability;
2. high accuracy that could be further improved by double reading (rating of the orbitofrontal patterns by two raters independently from each other, and then, by comparing and discussing the results).

3.2.1.3 Disadvantages of manual methodology

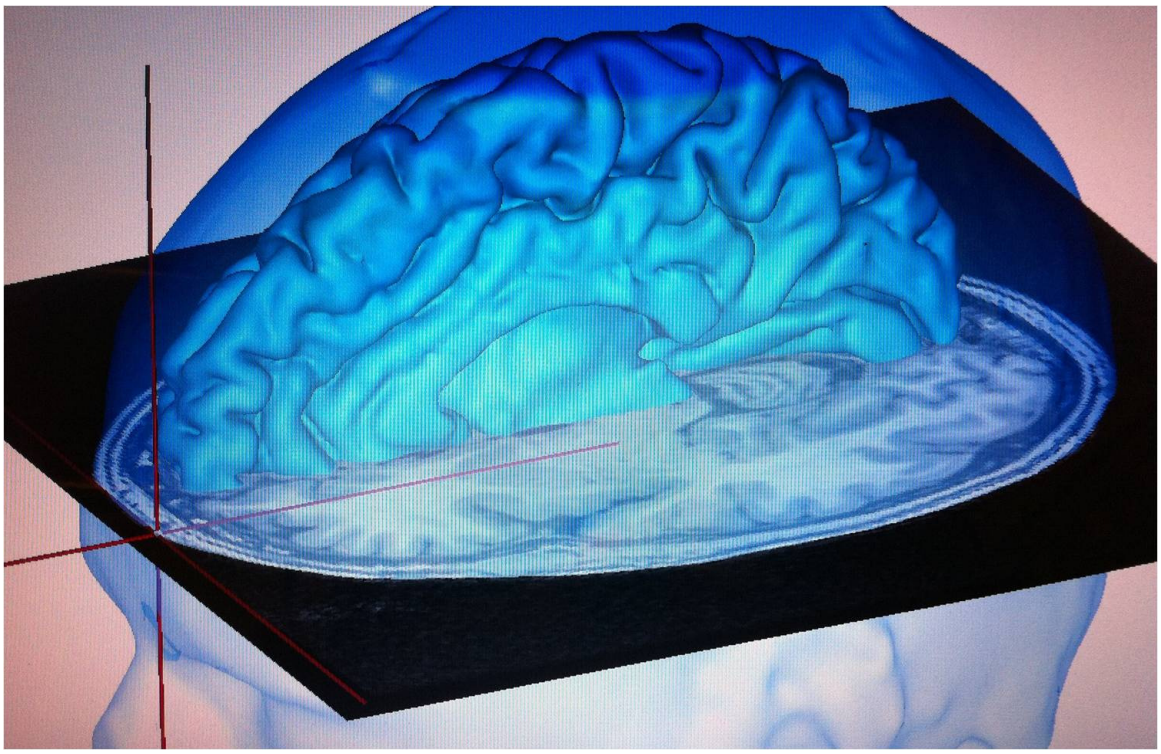
Disadvantages of manual methodology are:

1. required long training;
2. depends on individual's knowledge and ability to be attentive, patient and accurate;
3. time consuming.

3.2.2 Automatic sulci recognition

Automatic sulci recognition was performed using the BrainVISA software (http://brainvisa.info/; See **Figure 3.3**). This software identified sulci throughout the whole brain, including orbital sulci (See **Figure 3.4**). This process took around 30 minutes for each scan and required manual correction.

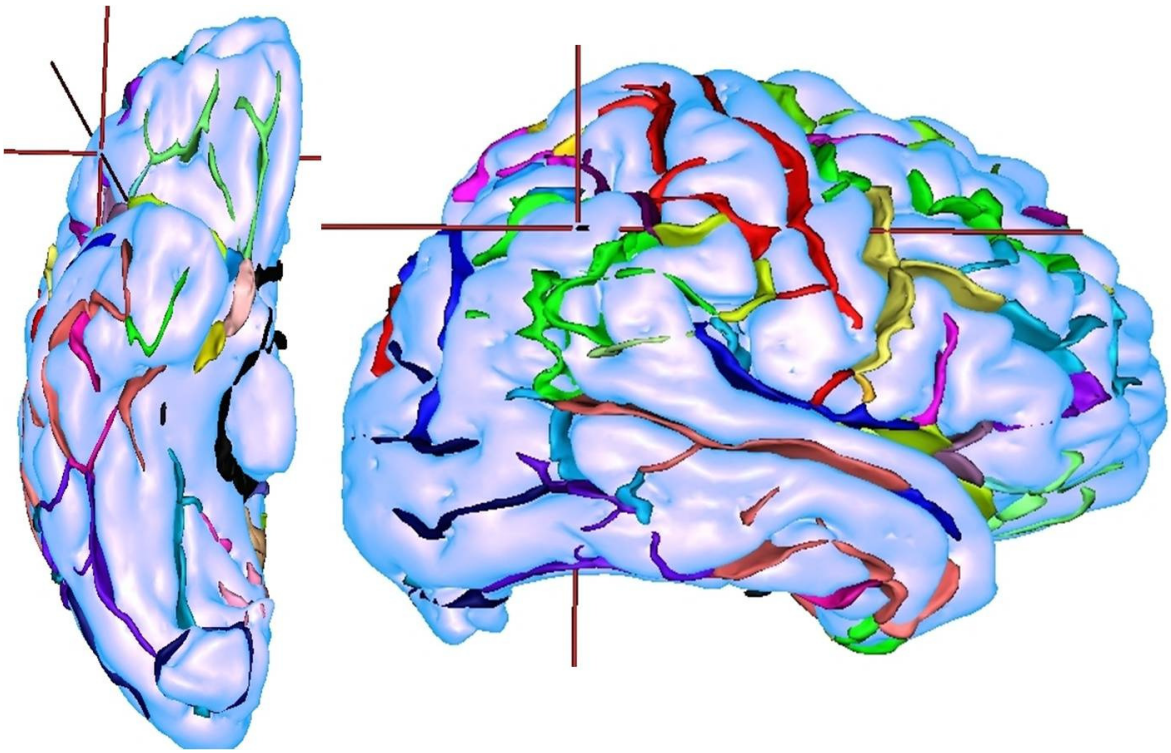
Figure 3.3. Image of the human brain by the BrainVISA software.



3.2.2.1 The BrainVISA software: the preprocessing steps

In order to evaluate the reliability of the automatic sulci recognition and manual protocols 20 out of 192 structural images of participants involved in this study were randomly selected and imported into the BrainVISA database where they were then processed using the BrainVISA sulcal identification pipeline (See **Figure 3.5**). Preparation of the raw T1 MRI data for the sulci identification pipeline requires the following:

Figure 3.4. This is an example of automatic sulci recognition that was performed using the BrainVISA software.



1. Importing the raw images into the BrainVISA database;

2. Preparation of the subjects, which includes the positioning of reference points (Anterior Commissure, Posterior Commissure, interhemispheric point and the left hemisphere point) and to reorient the image if necessary;

3. Pipeline Segmentation, which is based on two main algorithms: 3-D erosion and template - based 3 - D seed growth techniques and consists of T1 bias correction, histogram analysis, calculation of the brain mask, brain mask segmentation (separating white and grey matter), splitting the brain mask into two hemipspheres and the cerebellum, Talairach transformation,

computing oversampled MR image to improve cortical surface definition (cubic spline), computing oversampled Voronoj diagram (nearest neighbour), creating and smoothing mesh of each hemisphere and of the head, computing skeleton and buried gyrus watershed, and building Attributed Relational Graph (Rivière *et al.,* 2002; Cachia *et al.,* 2003; Mangin *et al.,* 2004 a, b);

4. Automatic labeling of sulci (Mangin *et al.,* 2004 b; Perrot *et al.,* 2011).

The following is the description of the third step in greater details:

- ***Estimation of a smooth multiplicative field***

Estimation of a smooth multiplicative field allowed the overcoming of the spatial inhomogeneities induced by the limitation of the acquisition process (Mangin, 2000).

- ***The analysis of intensity distribution***

This step provided an understanding of the statistics of white and grey matter by converting raw T1 - weighted MRI into the fold - based graphs using a scale - space based approach (Mangin *et al.,* 1998).

- ***Binarizing the image***

This step facilitated the determining of the range of intensities belonging to the brain by running a first sequence of erosion. Firstly, the brain mask was created and, then, by the erosion process, the seeds were defined from the outer surface of the head with the largest connected component not intersecting a layer of 5 mm. The reconstruction of those seeds was provided by a conditional dilatation in order to restore the shape of the brain (Mangin *et al.,* 1998).

- ***Splitting the brain mask into hemispheres and cerebellum***

At this stage a second sequence of erosion and conditional reconstruction were performed (Mangin *et al.,* 1996). Firstly, a white matter mask was defined by using a second binarization. Then, virtual normalization to Talairach's space was applied in order to stop the erosion process. A template image of another brain with hemispheres and cerebellum already split assisted in identifying at least one of the three components, usually the cerebellum, in the processing brain. At this point, the erosion was terminated and the reconstruction process was initiated. The cerebellum played a seed role for the reconstruction process.

- ***Defining the brain hull***

At this step the inner surface of the cortex was segmented from the brain hull. The brain hull was defined from a morphological closing. The intensity statistics was applied to define the grey and white matter interface. The parallelepipedic shape of the hemisphere was transformed into the object of interest by additions or deletions of topologically simple points (Mangin *et al.,* 1995).

- ***Skeletonization of the hollow object***

The skeletonization process was carried out by using the homotopic erosion method. The localization of the skeleton was defined by the intensity differences. The curvature was calculated based on the intensities. The erosion helped to preserve the spherical topology of the brain surface by filling holes in the curvature. A point of the skeleton was created at the surface point (Mangin *et al.,* 1995).

- ***Assembling and classifying of the skeleton points***

At this stage some of the skeleton points were connected to the outside and assembled together to represent the brain hull. The other parts of the

skeleton were classified into additional points: surface points, edge points and junction points.

- ***Combining of the surface points***

At this stage surface points were combined into topologically simple pieces of surface without any junctions (Mangin *et al.,* 1995).

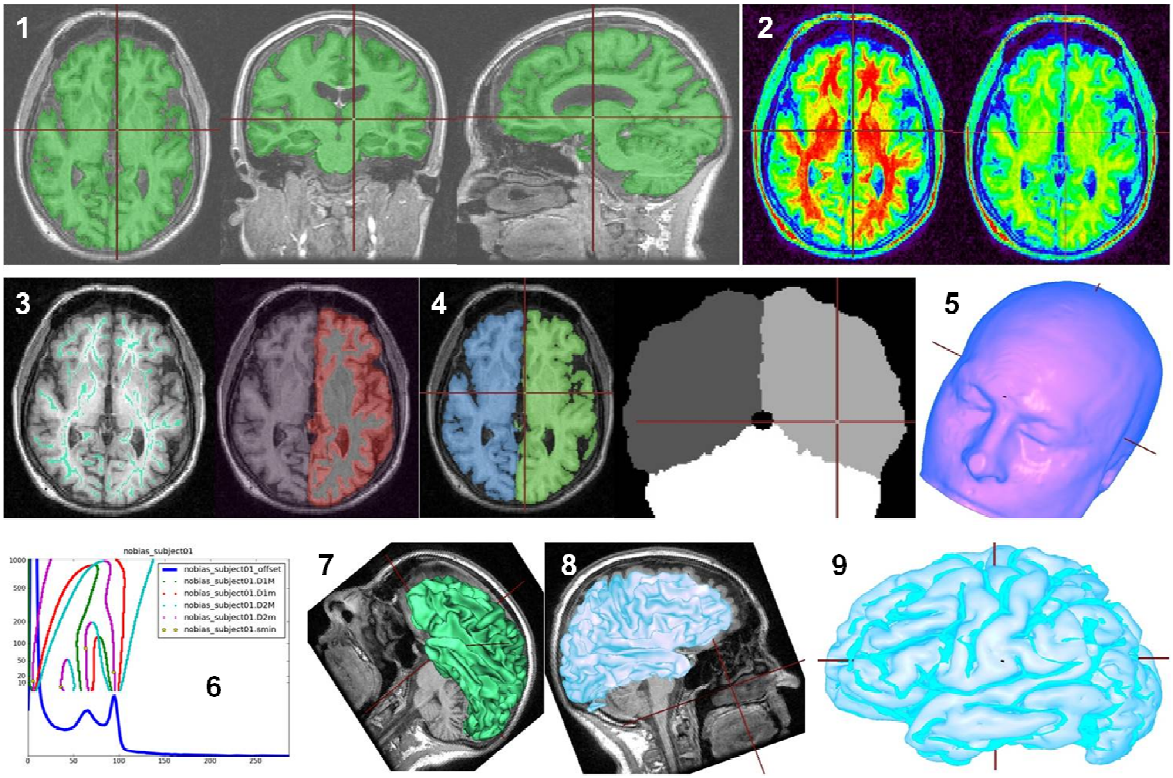
- ***Identifying of the buried gyri***

At this step previously created pieces of surface were split in order to identify gyri buried in the bottom of a fold. To achieve this, the Gaussian curvature of the magnetic resonance volume was computed and mapped on the brain inside interface. Then, connection of each voxel to the inside was analysed with the following deletion of a negative Gaussian curvature. After that the system of the geodesic depth was computed where the buried gyri help to generate boundaries. According to this parcellation, each simple surface was split.

- ***A graph structure***

Pieces of surface mapped in the previous stage were combined into a graph structure (Mangin *et al.,* 1995). This process was based on analysing three kinds of relationships: topological junctions, the buried gyri induced split and the geodesic to the brain hull neighbour which was computed using the Voronoj diagram. The calculation of the Voronoj diagram was based on the junctions with the folds that were used as seeds (Cachia *et al.,* 2003).

Figure 3.5. Steps of automatic sulci identification by the BrainVISA software. 1 = The brain mask; 2 = Corrected MRI (bias correction); 3 = White wridges and left hemicortex; 4 = Split mask and Voronoj template; 5 = Head mesh; 6 = Histogram analysis; 7 = The left white mesh; 8 = The right white mesh; 9 = The left graph.



3.2.2.2 Advantages of applying the automatic sulci recognition pipeline

Advantages of the automatic sulci recognition method are the following:

1. It saves a lot of time;
2. similar to a manual protocol, it examines connectivity of sulci;
3. it does not require the achievement of reliability.

3.2.2.3 Disadvantages of applying the automatic sulci recognition pipeline

Disadvantages of the automatic sulci recognition method are the following:

1. the BrainVISA software does not rate the orbitofrontal patterns, therefore this is a semi - automated protocol;
2. manual corrections of identified sulci are necessary;
3. a training is required to use the software;
4. the reliability between the manual and semi - automated protocol is lower than between two manual ratings.

3.2.2.4 Perspectives of automatic sulci identification methods

Perfected automatic sulci recognition and orbitofrontal patterns identification protocol may allow usage of the predictive orbitofrontal and anterior cingulate patterns in high risk population by any radiologist.

3.3 Distribution of orbitofrontal sulcogyral pattern in patients with bipolar affective disorder and schizophrenia

Distribution of the orbitofrontal sulcogyral patterns in patients with schizophrenia was previously reported by Nakamura and colleagues (2007). He found that the orbitofrontal type I was reduced while the orbitofrontal type III was increased in the right hemisphere in those with schizophrenia compared to healthy controls. He also discovered that the orbitofrontal type III in any hemisphere was associated with poorer socioeconomic status, more severe psychotic symptoms, poorer cognitive function and greater impulsivity when patients with type III were compared to patients without type III in any hemisphere. So far there was not any publication found that describes the distribution of orbitofrontal patterns in patients with bipolar affective disorder.

3.4 Methods

3.4.1 Participants

Recruitment procedures and patients' characteristics were previously reported elsewhere (McIntosh *et al.,* 2004). Briefly, one hundred and ninety two participants were involved in this study: forty nine healthy controls, twenty six age - matched patients with schizophrenia and forty five patients with bipolar affective disorder were identified from the case notes of the Royal Edinburgh Hospital. Unaffected relatives of these patients were also invited to participate. Detailed demographic statistics are presented in **Figure 3.9**.

All participants were subdivided into seven groups according to their diagnostic status and family history:

1. Healthy controls;
2. Patients with schizophrenia who were fulfilling the criteria of the DSM - IV for schizophrenia and who had at least one first - or second - degree relative with schizophrenia and no relatives known to be affected by bipolar disorder (in other words, who had family history of schizophrenia only);
3. Patients with bipolar I affective disorder, who were satisfying the criteria of DSM - IV for bipolar I disorder and who had at least one first - or second - degree relative with bipolar disorder and no relatives known to be affected by schizophrenia (in other words, who had family history of bipolar disorder only);
4. Patients with bipolar I affective disorder from mixed families who fulfilled the DSM - IV criteria for bipolar I disorder with at least one first - or second - degree relative with schizophrenia and at least one first - or second - degree relative with bipolar disorder;

5. Healthy adult volunteers with at least two first - or second - degree relatives with schizophrenia and without any relatives known to be affected by bipolar disorder (unaffected relatives of patients with schizophrenia);
6. Healthy adult participants with at least two first - or second - degree relatives with bipolar disorder and without any relatives known to be affected by schizophrenia (unaffected relatives of patients with bipolar affective disorder);
7. Healthy adult volunteers with at least one first - or second - degree relative with schizophrenia and at least one first - or second - degree relative with bipolar disorder (in other words, unaffected relatives from so called mixed families). They were recruited to investigate whether the effects of genetic liability to either disorder were specific to a particular orbitofrontal phenotype.

All participants were interviewed using the Present State Examination version 9 (PSE) (Wing *et al.,* 1974) in order to supplement the information obtained from case notes and to verify the diagnostic status of the subjects. The schedule for affective disorders and schizophrenia, lifetime version (SADS-L) was applied in order to further confirm the status of unaffected relatives (Endicott and Spitzer, 1978).

3.4.2 The Present State Examination (PSE)

In order to categorize the current symptoms all participants of this study were interviewed using the version 9 of the PSE (Wing *et al.,* 1974). This examination allowed placing the symptoms into one of the following categories:

1. No symptoms;
2. Unspecified symptoms from the PSE not rated in groups 2 and 4 below;

3. Any partially rated psychotic symptoms from the PSE sections 55 – 92 or 49 – 54;
4. Any fully rated psychotic symptoms from the PSE sections 55 – 92 or 49 – 54.

3.4.3 The Rivermead Behavioural Memory Test (RBMT)

This test was originally designed to examine a memory of individuals with acquired, non - progressive brain injury and described in Wilson and colleagues (1989). The RBMT includes tasks that are based on the everyday living situations as they are often difficult for people with impaired memory. This test is sensitive to the effects of age and IQ. This task consisted of the following eleven subtests: 'face recognition', 'story', 'first and second names', belongings', 'appointments', 'picture recognition', route and messages', and 'orientation and time'. During this test the stimuli were presented in standing books in such a way that the tester was able to read the relevant instructions while reviewing a miniature representation of each stimulus at the same time as this stimulus was presented to the participant (De Wall *et al.,* 1994).

3.4.4 The Young Mania Rating Scale

All participants were assessed using the Young Mania Rating Scale (Y-MRS; Young *et al.,* 1978). This was an eleven item rating scale conducted to a face-to-face interview (See **Figure 3.6**).

Figure 3.6. The Young Mania Rating Scale.

Items	Rating scale
Elevated mood	0. Absent
	1. Mildly or possibly increased on questioning
	2. Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
	3. Elevated, inappropriate to content; humorous
	4. Euphoric, inappropriate laughter
Increased motor activity - energy	0. Absent
	1. Subjectively increased
	2. Animated; gestures increased
	3. Excessive energy; hyperactive at times; restless (can be calmed)
	4. Motor excitement; continuous hyperactivity (cannot be calmed)
Sexual interest	0. Normal; not increased
	1. Mildly or possibly increased
	2. Definite subjective increase on questioning
	3. Spontaneous sexual content; elaborates on sexual matters
	4. Overt sexual acts (towards patients, staff or interviewer)
Sleep	0. Reports no decrease in sleep
	1. Sleeping less than normal amount by up to one hour
	2. Sleeping less than normal amount by more than one hour
	3. Reports decreased need for sleep
	4. Denies need for sleep
Irritability	0. Absent

	2. Subjectively increased
	4. Irritable at times during interview; recent episodes of anger or annoyance on ward
	6. Frequently irritable during interview; short, curt throughout
	8. Hostile uncooperative; interview impossible
Speech (rate and amount)	0. No increase
	2. Feels talkative
	4. Increased rate or amount at times; verbose at times
	6. Rush; consistently increased rate and amount; difficult to interrupt
	8. Pressured; uninterruptible, continuous speech
Language – Thought Disorder	0. Absent
	1. Circumstantial; mild distractibility; quick thoughts
	2. Distractible; looses goal of thought; changes topic frequently; racing thoughts
	3. Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
	4. Incoherent; communication impossible
Content	0. Normal
	2. Questionable plans, new interests
	4. Special projects, hyperreligious
	6. Grandiose or paranoid ideas; ideas of reference
	8. Delusions or hallucinations
Disruptive – Aggressive Behaviour	0. Absent, cooperative
	2.Sarcastic; loud at times, guarded
	4.Demanding, threats on ward
	6.Threatens interviewer, shouting; interview difficult
	8. Assaultive, destructive; interview impossible

Appearance	0. Appropriate dress and grooming
	1. Minimally unkempt
	2. Poorly groomed; moderately dishevelled; overdressed
	3. Dishevelled; partly clothed; garish make-up
	4. Completely unkempt; decorated; bizarre gard
Insight	0. Present
	1. Possibly ill
	2. Admits behaviour change but denies illness
	3. Admits possible behaviour change, but denies illness
	4. Denies any behaviour change

3.4.5 The Hamilton Depression Rating Scale

The Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) is a rating scale that is consisted of a 21 items and was completed at face - to - face interview with participants. Each item represents a sign or symptom that was rated according to an ordinal scale (See **Figure 3.7**). A total score was generated by adding the score from each item. The total score is believed to reflect the severity of depressive symptoms.

Figure 3.7. Items of the Hamilton Depression Rating Scale.

Item	Description
1	Depressed mood
2	Feelings of guilt
3	Suicide
4	Insomnia early
5	Insomnia middle
6	Insomnia late
7	Work and activities
8	Retardation: psychomotor
9	Agitation
10	Anxiety (psychological)
11	Anxiety (somatic)
12	Somatic symptoms (gastrointestinal)
13	Somatic symptoms (general)
14	Genital symptoms
15	Hypochondriasis
16	Loss of weight
17	Insight
18	Diurnal variation
19	Depersonalization and derealisation
20	Paranoid symptoms
21	Obsessional and compulsive symptoms

3.4.6 The Wechsler Abbreviated Scale of Intelligence

The Wechsler Abbreviated Scale of Intelligence (WASI) was applied to examine current intellectual functioning. The WASI consists of 4 subscales including block design, similarities, vocabulary, and matrix reasoning. They were designed to provide reliable and accurate measures of full scale, performance and verbal IQ. The WASI was completed during a face - to - face interview with a participant. There was an accompanying text that provided with the instructions for the administration and scoring of each subtest. During the vocabulary subtest the participants were asked to define a word that was presented to them verbally. During the block design subtest the participants require to arrange a series of 4 or 9 coloured blocks within a pre-specified period of time in such a way that they would fit a template pattern. During the similarities subtest the participants were required to define a rule that would explain the similarities between two items. During the matrix reasoning subtest the participants were asked to look at a matrix of items with a single item from this matrix missing. The participant will have to complete the pattern by selecting an item from the list.

3.4.7 The National Adult Reading Test

The National Adult Reading Test (NART) is a commonly used method in psychological practice and research for estimation of premorbid intelligence levels and up-to-date remains one of the most reliable tests (Nelson, 1982; Crawford *et al.,* 1989). This test was originally designed to examine the premorbid IQ of individuals with the suspected intellectual decline. Existing evidence suggests that performance on the NART is correlated with the general factor of intelligence from the Wechsler scales and may provide a valid estimation of Intelligence Quotient (IQ) (Crawford *et al.,* 1989). There are several versions of this test including a revised NART - R, a Swedish-language version NART - SWE and a New Zealand version NZART. The

version that was used in the studies analysed in the thesis consisted of 50 short words that have atypical grapheme-phoneme conversions. See the examples of the words that were used to evaluate premorbid intelligence in the EHRS in **Figure 3.8**. Each word was presented in order of increasing difficulty. The participants were asked to read the list of words of irregular pronunciation aloud. In order to be able to perform this test successfully, participant had to have prior knowledge of those words pronunciation. Otherwise, they would not be able to read the words accurately. The premorbid IQ of the participants was estimated according to the number of correctly pronounced words (or to the number of made pronunciation errors).

Figure 3.8. The National Adult Reading Test.

Abstemious	Gist
Ache	Gouge
Aeon	Heir
Aisle	Hiatus
Assignate	Idyll
Aver	Labile
Banal	Leviathan
Beatify	Naïve
Bouquet	Nausea
Campanile	Placebo
Capon	Prelate
Catacomb	Procreate
Cellist	Psalm
Chord	Puerperal
Courteous	Quadruped
Debt	Radix
Demesne	Rarefy
Deny	Sidereal
Depot	Simile
Detente	Subtle
Drachm	Superfluous
Equivocal	Syncope
Facade	Thyme
Gaoled	Topiary
Gauche	Zealot

3.4.8 MRI scanning

Each participant was scanned on a 1,5 - Tesla GE MRI scanner (GE Medical Systems, Milwaukee, Wisconsin). Midline sagittal localization was followed by two further sequences to image the whole brain. The first sequence was a transverse spin - echo scan, which acquired both T2 - and proton density - weighted images of the brain. The final sequence was a coronal gradient echo sequence with magnetization preparation and produced 128 coronal high - resolution T1 - weighted images, which were used for structural analysis (time of inversion [TI] = 600 msec, echo time = 3.4 msec, flip angle = 15°, field of view = 22, slice thickness = 1.7 mm, matrix = 256 x 192). Images were converted into ANALYZE 3 - D file format for further processing.

3.4.9 Identification of the orbitofrontal patterns

The manual orbitofrontal sulcogyral pattern identification protocol was developed based on the one proposed by Chiavaras and Petrides (2000) and further enhanced with the orbitofrontal type IV (Chakirova *et al.,* 2010). More detailed protocol could be found in the **Appendix III** of this thesis. See also **Figure 1.4** in **Chapter 1** of this thesis.

3.4.10 The reliability of the manual orbitofrontal sulcogyral pattern identification protocol

The classification of the orbitofrontal sulcogyral patterns was carried out by two raters independently, blinded to subject group. Inter - rater reliability was assessed by evaluating the sulcal patterns of 15 random cases (30 hemispheres: 15 in the right and 15 in the left hemispheres). The intra - class correlation coefficients were 0.86 for right hemisphere and 0.84 for left hemisphere. Moreover, two raters (including GC) evaluated the orbitofrontal cortex in three hundred and eighty four hemispheres independently and then

compared and discussed the results. Any disagreements about the orbitofrontal pattern ratings were resolved by discussion until consensus was reached.

3.4.11 The protocol of classification of the anterior cingulate morphology

To perform the CS and PCS classification protocol, firstly, the medial brain surface sulci were identified using the "MRIcro" software package freely available on http://www.sph.sc.edu/comd/rorden/mricro.html, then confirmed and measured using "Analyze" software (Mayo Foundation, Rochester, MN).

There are two previously developed protocols of ACC classification: Paus' and Yücel's protocols (Paus *et al.,* 1996; Yucel *et al.,* 2001). The difference between two protocols is in the variety of the sulcal forms included into the classification categories (Leonard *et al.,* 2009). In order to classify the CS and PCS in this study the criteria described by Yucel and colleagues (2001) was applied as this protocol is known to be more reliable (Leonard *et al.,* 2009). This protocol was obtained from the authors; also described in references (Slagle *et al.,* 1989; Rahm *et al.,* 2006; Broome *et al.,* 2009). In order to identify the paracingulate and cingulate sulci from 3 to 4 consecutive sagittal slices were examined starting from the interhemispheric fissure and moving laterally into the brain tissue. According to the protocol sulcal segments had to be evident and distinguishable from the superficial cortical dimples. The correct identification of each sulcus had to be confirmed using the axial and coronal sections of the brain. This helped to exclude superficial cortical dimples from the analyses.

The cingulate sulcus was considered to be interrupted into segments if there was present a clear gap on several sagittal sections (Leonard *et al.,* 2009). Importantly, this gap had to be confirmed using coronal section; otherwise

the cingulate sulcus was identified as a single or continuous sulcus. The number of segments of the cingulate sulcus was recorded counting from the sulcus origin anterior to the genuine of the corpus callosum to its posterior marginal ramus branch.

The paracingulate sulcus was identified using the sagittal slices as this sulcus starts immediately dorsal and runs parallel to the cingulate sulcus. Following the previously developed protocol (Yucel *et al.,* 2001) the PCS morphological variants were subdivided into three groups according to their anterior - posterior extent and their presence:

1. The PCS variant was named 'prominent' if it was more than 40 mm in length;
2. The PCS variant was called 'present' when the sulcus piece(s) were more than 20 mm in length;
3. The PCS variant was considered to be 'absent' if PCS was not identifiable at all or it was less than 20 mm in length.

There were some other details in the protocol regarding to the rating of the PCS morphological variants. For example, only the PCS segments that were more than 10 mm in length were included. In order for the PCS variant to be classified as 'present' at least one segment supposed to be about 20mm in length. Where a single segment was more than 40 mm in length the PCS was rated as 'prominent'. However, when the total length of the PCS was more than 40 mm but the total gaps between segments were measured more than 20 mm this morphological PCS variant was rated as 'present'.

3.4.12 The reliability of the anterior cingulate morphology identification protocol

Two raters used the protocol until confident and then rated the same 25 randomly chosen scans (50 hemispheres). Left/right inter - rater reliability was 1.00/0.933 for CS classification and 0.80/0.80 for PCS classification respectively. Then, one rater proceeded with the classification of the cingulate sulcus, while the other rater identified the paracingulate sulcus on the 216 images (432 hemispheres) in this study. Left/right intra - rater reliability was assessed in a subset of 15 scans (30 hemispheres) and were 1.00/1.00 for the cingulate and 0.91/0.87 for the paracingulate sulcus classification.

3.4.13 Statistics

All statistical analyses were performed using the Statistical Program for the Social Sciences (SPSS, Chicago, Illinois) version 19 (http://www.spss.com/software). Demographics (age, sex, handedness, IQ and duration of illness) were compared using Fisher's exact test for categorical values and by applying regression analysis for continuous values. The distribution of types I, II, III and IV sulcogyral patterns in either hemisphere in various groups was compared by applying Kruskal - Wallis test.

Twenty randomly selected scans were processed using the automatic sulci identification pipeline of the BrainVISA software. The identification of the orbital sulci and their labelling were manually corrected and the orbitofrontal pattern was classified according to connectivity and continuity of the orbital sulci. The results obtained by manual and automatic protocols were compared by calculating intraclass correlation coefficients for the right and left hemispheres.

It was also considered to be important to examine whether there are any differences in distribution of symmetric and asymmetric scans. Brain structural scans were classified as symmetric if there was the same orbitofrontal pattern in the right and in the left hemisphere (type I in the right hemisphere and type I in the left hemisphere, type II in the right hemisphere and type II in the left hemisphere, type III in the right hemisphere and type III in the left hemisphere, type IV in the right hemisphere and type IV in the left hemisphere). All the other scans possessing different orbitofrontal patterns in the left and the right hemispheres were identified as asymmetric scans.

The gender effect on the distribution of the orbitofrontal and anterior cingulate morphology, the symmetry – asymmetry comparison of the orbitofrontal and anterior cingulate morphology between the groups, the distribution of the cingulate and paracingulate sulcul morphological variants between the groups, associations between orbitofrontal and anterior cingulate morphology, and neuropsychological and structural associations of the orbitofrontal morphology were analysed using Kruskal - Wallis test. The positive and negative predictive values as well as sensitivity and specificity were calculated.

3.5 Results

3.5.1 Demographics

There was no statistically significant difference found between the groups in age, gender, handedness and IQ. Moreover, patients with schizophrenia and bipolar affective disorder did not differ in the duration of their illness (See **Figure 3.9***).*

Figure 3.9. Demographic characteristics. HC = Healthy controls, SCH = patients with schizophrenia, UR = Unaffected Relatives, BPD = Bipolar Disorder, SCH Family = Family history of Schizophrenia, BPD Family = Family history of Bipolar Disorder, MIX Family = Family history of both Schizophrenia and Bipolar Disorder.

Group	HC	SCH from SCH Family	UR from SCH Family	BPD from BPD Family	UR from BPD Family	BPD from MIX Family	UR from MIX Family	χ^2	p value
No	49	26	24	26	22	19	26		
R hand preference No (%)	46 (93.9)	23 (88.5)	20 (83.3)	24 (92.3)	21 (95.5)	19 (100)	24 (92.3)	5.165	0.523
Male No (%)	23 (46.9)	13 (50)	11 (45.8)	14 (53.9)	9 (40.9)	7 (36.8)	14 (53.9)	1.983	0.921
NART IQ Mean (SD)	110.5 (8.7)	100.5 (12.3)	102.7 (10.2)	111.1 (10.9)	105.6 (10.3)	105.7 (11.0)	105.0 (9.8)	28.06	0.061
								F	P value
Age Mean (SD)	35.27 (11.1)	36.85 (13.7)	38.92 (12.9)	40.5 (12.1)	34.73 (12.6)	39.74 (9.2)	34.12 (13.0)	1.138	0.342
Height Mean (SD)	1.72 (.1)	1.70 (.1)	1.67 (.1)	1.70 (.1)	1.70 (.1)	1.69 (.1)	1.71 (.1)	0.900	0.496

3.5.2 Reliability between manual and automatic sulci recognition

Twenty randomly chosen T1s from the present study were pre - processed using the BrainVISA software. Then, the automatic recognition of the orbitofrontal sulcogyral morphology was compared with the manually identified orbitofrontal patterns in the same images. The intraclass correlation coefficients between manual and automatic protocol were 0.75 for the left hemisphere and 0.74 for the right hemisphere.

3.5.3 Distribution of the orbitofrontal sulcogyral pattern in each group (See Figure 3.10)

Considering the better reliability of the manual protocol and the fact that the BrainVISA software only identifies sulci but does not provide with the actual classification of the orbitofrontal patterns it was decided to select the manual protocol to investigate further the orbitofrontal morphology.

Two groups in the Psychosis study were used as controls in order to validate the manual sulcogyral pattern identification protocol: healthy volunteers and patients with schizophrenia given that the distribution of the orbitofrontal sulcogyral patterns in healthy population and patients with schizophrenia was previously reported elsewhere (Chiavaras and Petrides, 2000; Nakamura *et al.,* 2007; Chakirova *et al.,* 2010). It was considered especially important to assess the alteration of the orbitofrontal morphology in patients with bipolar disorder and in the unaffected relatives of patients with bipolar disorder and schizophrenia given that this was not previously established. The hypothesis was that there might be difference in the distribution of orbitofrontal patterns between patients with bipolar disorder from the bipolar families and patients with bipolar disorder from the mixed families if orbitofrontal morphology is indeed genetically determined.

Figure 3.10. Distribution of Chiavaras' Types I - III within the groups. HC = healthy controls, SCH = patients with schizophrenia, UR = unaffected relatives, BPD = bipolar disorder, SCH Family = family history of schizophrenia, BPD Family = family history of bipolar disorder, MIX Family = family history of both schizophrenia and bipolar disorder. The numbers in red colour are those where a significant difference was found.

	SN	Type I RH		Type II RH		Type III RH		Type I LH		Type II LH		Type III LH	
		No	%	No	%	No	%	No	%	No	%	No	%
HC	49	31	67	10	22	5	11	25	51	16	33	8	16
SCH from SCH Family	26	12	46	6	23	8	**31**	13	52	7	28	5	20
UR from SCH Family	24	14	58	7	29	3	13	12	50	8	33	4	17
BPD from BPD Family	26	12	50	5	21	7	**29**	8	33	7	29	9	**38**
UR from BPD Family	22	14	67	5	24	2	9	11	50	7	32	4	18
BPD from MIX Family	19	9	47	5	26	5	**27**	7	37	6	31	6	**32**
UR from MIX Family	26	15	60	7	28	3	12	13	52	7	28	5	20

First of all, the observed sulcal pattern distribution in the 49 healthy control subjects was similar on the left hemisphere and on the right hemisphere to that reported in healthy Canadian populations by Chiavaras and Petrides (2000).

There was a significantly increased prevalence of type III in the right hemisphere in the schizophrenia group, compared to healthy controls (Kruskal - Wallis = 4.947, df = 1, p = 0.026), but not in the left hemisphere (Kruskal - Wallis = 0.099, df = 1, p = 0.753) in accordance to the results published by Nakamura and colleagues (2007).

The distribution of orbitofrontal patterns seen in unaffected relatives of people with schizophrenia and bipolar affective disorder is comparable to that in healthy controls: Kruskal - Wallis = 0.006, df = 1, p = 0.938 on the left hemisphere and Kruskal - Wallis = 0.024, df = 1, p = 0.876 on the right hemisphere in relatives of patients with schizophrenia, Kruskal - Wallis = 0.091, df = 1, p = 0.763 on the left hemisphere and Kruskal - Wallis = 0.000, df = 1, p = 0.982 on the right hemisphere in relatives of patients with bipolar disorder and with the family history of bipolar disorder only, and Kruskal - Wallis = 0.138, df = 1, p = 0.710 on the left hemisphere and Kruskal - Wallis = 0.107, df = 1, p = 0.744 on the right hemisphere in relatives of patients with bipolar disorder and with the family history of both bipolar disorder and schizophrenia.

When the bipolar disorder group with family history of bipolar disorder only was compared to the group of healthy controls, there was a significant difference found in distribution of the orbitofrontal patterns in the left hemisphere (Kruskal - Wallis = 5.500, df = 1, p = 0.019) with a trend to increased frequency of type III (Kruskal - Wallis = 3.198, df = 1, p = 0.074) and reduction of the orbitofrontal type I (Kruskal - Wallis = 2.790, df = 1, p =

0.095). There was also a trend to increased prevalence of type III in the right hemisphere (Kruskal - Wallis = 3.486, df = 1, p = 0.062).

When the bipolar disorder group with family history of both bipolar affective disorder and schizophrenia was compared to the group of healthy controls, there was a trend found towards increasing frequency of the orbitofrontal type III in the right hemisphere (Kruskal - Wallis = 2.792, df = 1, p = 0.095), but not in the left hemisphere (Kruskal - Wallis = 1.919, df = 1, p = 0.166).

There was a significant difference found in the distribution of the orbitofrontal type III in the left hemisphere when individuals with schizophrenia and bipolar disorder were compared (Mann - Whitney U = 260.000, p = 0.050) in a such a way that patients with bipolar disorder have greater number of type III in the left hemisphere than participants with schizophrenia.

There was a trend found in the distribution of the all orbitofrontal patterns in the left hemisphere (Kruskal - Wallis = 2.835, df = 1, p = 0.092) when patients with bipolar affective disorder and a family history of bipolar disorder only were compared to their unaffected relatives. The expression of type I and III in the right hemisphere of both bipolar disorder groups was similar to that in the schizophrenia group from schizophrenia family. However, in the left hemisphere of both bipolar disorder groups type III occurred more frequently than in the group of patients with schizophrenia having a familial history. Between two bipolar groups, the frequency of type III was higher in the bipolar group with a family history of only bipolar disorder in contrast to the bipolar group with family history of bipolar disorder and schizophrenia.

Figure 3.11. Distribution of symmetric and asymmetric scans in different diagnostic groups of the study. HC = healthy controls, SCH = patients with schizophrenia, UR SCH = unaffected relatives of patients with schizophrenia, BD = patients with bipolar disorder with family history of bipolar disorder only, UR BD = unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder only, BD mix = patients with bipolar disorder with family history of bipolar disorder and schizophrenia, UR BD mix = unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder and schizophrenia.

Groups	Symmetric Scans								Asymmetric Scans		Total
	Types I – I		Types II – II		Types III – III		Types IV - IV				
	No	%	No	%	No	%	No	%	No	%	No
HC	18	37	5	10	3	6	0	0	23	47	49
SCH	4	15	0	0	3	12	0	0	19	73	26
UR SCH	9	37	5	21	0	0	0	0	10	42	24
BD	6	23	2	8	4	15	1	4	13	50	26
UR BD	8	36	3	14	0	0	0	0	11	50	22
BD mix	4	21	2	10.5	2	10.5	0	0	11	58	19
UR BD mix	7	27	3	11	0	0	0	0	16	62	26

3.5.4 Gender effect on the distribution of the orbitofrontal morphology in different diagnostic groups

There was a significant difference found in the distribution of the orbitofrontal type III in the right hemisphere in males (Kruskal - Wallis = 5.476, df = 1, p = 0.019), but not in females (Kruskal - Wallis = 0.836, df = 1, p = 0.361) when healthy controls were compared to patients with schizophrenia. This suggests that the group difference in distribution of type III in the right hemisphere that was previously described in this chapter (Kruskal - Wallis = 4.947, df = 1, p = 0.026) might be associated with gender and originated in male participants.

There was a significant difference found in distribution of the orbitofrontal patterns in the right hemisphere (Kruskal - Wallis = 5.110, df = 1, p = 0.024) with increased frequency of type III (Kruskal - Wallis = 6.083, df = 1, p = 0.014) and reduction of type I in the right hemisphere (Kruskal - Wallis = 3.390, df = 1, p = 0.066) in male participants when healthy controls were compared to patients with bipolar disorder and a family history of bipolar disorder only. However, there was only a trend found in the distribution of the all orbitofrontal patterns in the left hemisphere in females (Kruskal - Wallis = 3.544, df = 1, p = 0.060), but not in males (Kruskal - Wallis = 0.492, df = 1, p = 0.483), coming from the distribution of the type III in the left hemisphere in females (Kruskal - Wallis = 2.784, df = 1, p = 0.095), when two groups were compared.

There was a significant difference found in distribution of the type III in the left hemisphere in females (Kruskal - Wallis = 4.192, df = 1, p = 0.041), additionally, with a trend in the distribution of the orbitofrontal type I in the right hemisphere in females (Kruskal - Wallis = 3.033, df = 1, p = 0.082) and with a trend related to appearance of type II in the left hemisphere (Kruskal - Wallis = 3.209, df = 1, p = 0.073) in females, but not in males when healthy

controls were compared to patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder.

There was a trend to significance found in distribution of the orbitofrontal type II in the left hemisphere in females (Kruskal - Wallis = 3.410, df = 1, p = 0.065) as well as in males (Kruskal - Wallis = 3.299, df = 1, p = 0.069) when healthy controls were compared to patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder.

There was a trend to significance found in distribution of the orbitofrontal type II in the left hemisphere in females (Kruskal - Wallis = 3.125, df = 1, p = 0.077) as well as in males (Kruskal - Wallis = 2.875, df = 1, p = 0.090) when patients with bipolar disorder and a family history of bipolar disorder only were compared to patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder.

There was a significant difference found in distribution of the orbitofrontal type III in the left hemisphere in females (Kruskal - Wallis = 4.000, df = 1, p = 0.046), but not in males (Kruskal - Wallis = 0.242, df = 1, p = 0.623) when patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder were compared to their unaffected relatives.

There was a trend to significance found in distribution of the orbitofrontal type II in the left hemisphere in males (Kruskal - Wallis = 2.778, df = 1, p = 0.096), but not in females (Kruskal - Wallis = 1.137, df = 1, p = 0.286) when patients with schizophrenia were compared to their unaffected relatives.

3.5.5 Orbitofrontal morphology: distribution of symmetric and asymmetric scans between different diagnostic groups of this study

Symmetry was analysed in a following way. All scans with the same orbitofrontal pattern in the right and in the left hemisphere (symmetric scans) were given a value of one. All the rest of the scans were named asymmetric and were given a value of zero. Distribution of the orbitofrontal patterns in symmetric and asymmetric scans in different diagnostic groups of this study is presented in **Figure 3.11**. The only significant difference in such symmetry was found between patients with schizophrenia and healthy volunteers (Kruskal - Wallis = 4.647, df = 1, p = 0.031) and between patients with schizophrenia and their unaffected relatives (Kruskal - Wallis = 4.953, df = 1, p = 0.026), with the schizophrenia patients being more asymmetric (73% of asymmetric scans) than the rest of the groups (47% of asymmetric scans in healthy controls and 42% of asymmetric scans in unaffected relatives of patients with schizophrenia) (See **Figure 3.12** for the rest of the groups). Although there was a trend in the orbitofrontal symmetry between patients with schizophrenia and patients with bipolar disorder (Kruskal - Wallis = 2.869, df = 1, p = 0.090), when patients with bipolar disorder tend to be more symmetric than patients with schizophrenia.

Figure 3.12. Comparison of symmetric versus asymmetric scans between different diagnostic groups in this study. HC = healthy controls, SCH = patients with schizophrenia, UR SCH = unaffected relatives of patients with schizophrenia, BD = patients with bipolar disorder with family history of bipolar disorder only, UR BD = unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder only, BD mix = patients with bipolar disorder with family history of bipolar disorder and schizophrenia, UR BD mix = unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder and schizophrenia.

Groups' Comparison	Kruskal-Wallis	df	P value
HC versus SCH	4.647	1	**0.031***
SCH versus UR SCH	4.953	1	**0.026***
HC versus BD	0.064	1	0.801
HC versus BD mix	0.657	1	0.417
BD mix versus UR BD mix	0.061	1	0.805
BD versus UR BD	0.000	1	1.000

***significant difference**

3.5.6 Summary

Analysis of the orbitofrontal sulcogyral patterns revealed an increased frequency of type III and a reduced frequency of type I in the right hemisphere in patients with schizophrenia and an increased frequency of type III in both right and left hemispheres with the reduction of type I in both hemispheres in patients with bipolar disorder compared to healthy controls. Importantly, these findings were replicated in the Edinburgh High Risk Study (See **Chapter 4** for details) and in the Bipolar Family Study (See **Chapter 5** for details). Patients with schizophrenia and bipolar disorder differed from

each other significantly in the distribution of type III in the left hemisphere. The distribution of the orbitofrontal sulcogyral patterns in unaffected relatives of patients with schizophrenia and bipolar disorder were similar to those in controls.

There was a gender effect found on the distribution of the orbitofrontal morphology suggesting that the distribution of the orbitofrontal patterns in the right hemisphere is more likely to be associated with males, while the distribution of the orbitofrontal patterns in the left hemisphere is more likely to be associated with females regardless what diagnostic groups were compared.

Other important finding was related to symmetry of the orbitofrontal patterning (having the same orbitofrontal patterns in both right and left hemispheres). Healthy individuals appeared to have more symmetric orbitofrontal cortex than patients with schizophrenia (this result was replicated in the Edinburgh High Risk Study, see **Chapter 4** for details). Unlike patients with schizophrenia, patients with bipolar disorder were as symmetric as healthy controls regarding the distribution of the orbitofrontal sulcogyral patterns.

3.5.7 Distribution of the cingulate and paracingulate sulci in different diagnostic groups of this study

Given that the cingulate sulcus is always present the morphological variants of the cingulate sulcus were examined in patients with bipolar disorder, schizophrenia and their unaffected relatives. The existing accepted classification of the anterior cingulate morphology was based on the continuity of the cingulate sulcus that is whether it has a single continuous form or is fragmented into pieces. So the number of the cingulate sulcus (CS) pieces was compared between the groups. There was no significant

difference found in distribution of the CS pieces between healthy controls and patients with schizophrenia in both the left (Kruskal - Wallis = 0.135, df = 1, p = 0.713) and right (Kruskal - Wallis = 1.534, df = 1, p = 0.216) hemispheres. However, even if it did not reach significant level, it was noticeable that control individuals tended to have a single continuous CS in both hemispheres, while patients with schizophrenia were more likely to have a 'disconnected' ('broken') CS with 2 or 3 pieces (segments).

With both males and females included there was no difference found in the distribution of the paracingulate sulcus variants in the right (Kruskal - Wallis = 1.218, df = 1, p = 0.270) or in the left hemisphere (Kruskal - Wallis = 0.204, df = 1, p = 0.651) when healthy individuals and patients with schizophrenia were compared.

With both males and females included patients with schizophrenia were compared to their unaffected relatives. There was no significant difference found in distribution of the CS pieces between patients with schizophrenia and their unaffected relatives in both the left (Kruskal - Wallis = 0.050, df = 1, p = 0.824) and right (Kruskal - Wallis = 0.147, df = 1, p = 0.701) hemispheres. With both males and females included there was a significant difference found in the distribution of the prominent paracingulate sulcus variant in the left hemisphere (Kruskal - Wallis = 3.898, df = 1, p = 0.048) when patients with schizophrenia were compared to their unaffected relatives.

With both males and females included patients with bipolar disorder and a family history of bipolar disorder only (group 4) were compared to their unaffected relatives (group 5). There was no significant difference found in distribution of the CS pieces between patients with bipolar disorder and a family history of bipolar disorder and their unaffected relatives in both the left (Kruskal - Wallis = 1.549, df = 1, p = 0.213) and right (Kruskal - Wallis =

1.829, df = 1, p = 0.176) hemispheres. With both males and females included there was a significant difference found in the distribution of the paracingulate sulcus in the left hemisphere (Kruskal - Wallis = 8.059, df = 1, p = 0.005) with increased frequency of the prominent variant of the PCS (Kruskal - Wallis = 5.826, df = 1, p = 0.016) and reduced frequency of the absent variant of the PCS (Kruskal - Wallis = 11.125, df = 1, p = 0.001) in unaffected relatives of the patients with bipolar disorder when compared to patients themselves.

Similarly both males and females patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder (group 6) were compared to their unaffected relatives (group 7). There was no significant difference found in distribution of the CS pieces between patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder and their unaffected relatives in both the left (Kruskal - Wallis = 0.601, df = 1, p = 0.438) and right (Kruskal - Wallis = 0.272, df = 1, p = 0.602) hemispheres. For males and females taken together there was a trend found in the distribution of the present paracingulate sulcus variant in the left hemisphere (Kruskal - Wallis = 3.137, df = 1, p = 0.077) with increased frequency of the present PCS in unaffected relatives of the patients with bipolar disorder when compared to patients themselves.

For males and females patients with schizophrenia were compared to patients with bipolar disorder and a family history of bipolar disorder only (group 4). There was no significant difference found in distribution of the CS pieces between patients with bipolar disorder and a family history of bipolar disorder only and patients with schizophrenia in both the left (Kruskal - Wallis = 1.971, df = 1, p = 0.160) and right (Kruskal - Wallis = 0.217, df = 1, p = 0.641) hemispheres. With both males and females included there was a trend found in the distribution of the present paracingulate sulcus variant in the left hemisphere (Kruskal - Wallis = 2.957, df = 1, p = 0.086) with an

increased frequency of the present PCS in patients with schizophrenia when compared to patients with bipolar disorder.

For males and females patients with schizophrenia were compared to patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder. There was no significant difference found in distribution of the CS pieces between patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder and patients with schizophrenia in both the left (Kruskal - Wallis = 0.014, df = 1, p = 0.904) and right (Kruskal - Wallis = 1.163, df = 1, p = 0.281) hemispheres. With both males and females included there was a significant difference found in the distribution of the present paracingulate sulcus variant in the left hemisphere (Kruskal - Wallis = 4.019, df = 1, p = 0.045) with an increased frequency of the present PCS in patients with schizophrenia when compared to patients with bipolar disorder.

For males and females patients with bipolar disorder and a family history of bipolar disorder only were compared to patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder. There was no significant difference found in distribution of the CS pieces between both patient groups with bipolar disorder either in the left (Kruskal - Wallis = 1.261, df = 1, p = 0.261) or in the right (Kruskal - Wallis = 2.313, df = 1, p = 0.128) hemispheres. With both males and females included there was no difference found in the distribution of the paracingulate sulcus variants either in the left (Kruskal - Wallis = 0.280, df = 1, p = 0.597) or in the right hemisphere (Kruskal - Wallis = 0.036, df = 1, p = 0.850) when two bipolar groups were compared.

For males and females healthy controls were compared to unaffected relatives of patients with schizophrenia. There was a trend to significance found in distribution of the CS pieces between healthy controls and unaffected relatives of patients with schizophrenia in the right (Kruskal -

Wallis = 2.913, df = 1, p = 0.088), but not in the left (Kruskal - Wallis = 0.383, df = 1, p = 0.536) hemisphere in such a way that healthy individuals were more likely to possess the connected CS variant (presented as one piece) while unaffected relatives of patients with schizophrenia had more frequently the disconnected variant of the CS (presented as many pieces) in the right hemisphere. With both males and females included there was no difference found in the distribution of the paracingulate sulcus variants either in the left (Kruskal - Wallis = 2.555, df = 1, p = 0.110) or in the right hemisphere (Kruskal - Wallis = 0.364, df = 1, p = 0.546) when healthy individuals and unaffected relatives of patients with schizophrenia were compared.

For males and females healthy controls were compared to unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder only. There was no significant difference found in distribution of the CS pieces between healthy controls and unaffected relatives of patients with bipolar disorder either in the right (Kruskal - Wallis = 0.689, df = 1, p = 0.407) or in the left (Kruskal - Wallis = 0.021, df = 1, p = 0.885). With both males and females included there was a significant difference found in the distribution of the paracingulate sulcus variants in the left (Kruskal - Wallis = 9.054, df = 1, p = 0.003), but not in the right hemisphere (Kruskal - Wallis = 0.246, df = 1, p = 0.620) when healthy individuals and unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder only were compared in such a way that healthy individuals were more likely to possess the absent PCS variant (Kruskal - Wallis = 8.214, df = 1, p = 0.004) while unaffected relatives of patients with bipolar disorder were more likely to have the prominent PCS variant (Kruskal - Wallis = 7.634, df = 1, p = 0.006) in the left hemisphere.

For males and females healthy controls were compared to unaffected relatives of patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder. There was a trend to significance found

in distribution of the CS pieces between healthy controls and unaffected relatives of patients with bipolar disorder in the right (Kruskal - Wallis = 3.731, df = 1, p = 0.053), but not in the left hemisphere (Kruskal - Wallis = 1.498, df = 1, p = 0.221) in such a way that unaffected relatives of patients with bipolar disorder were more likely to possess the disconnected CS variant (presented in many pieces) (Kruskal - Wallis = 3.189, df = 1, p = 0.074) while healthy individuals are more likely to have the connected CS variant (presented as one piece) in the right hemisphere (Kruskal - Wallis = 3.189, df = 1, p = 0.074) when two groups were compared. With both males and females included there was no difference found in the distribution of the paracingulate sulcus variants either in the left (Kruskal - Wallis = 1.244, df = 1, p = 0.265) or in the right hemisphere (Kruskal - Wallis = 0.202, df = 1, p = 0.653) when healthy individuals and unaffected relatives of patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder were compared.

3.5.8 Gender effect on the distribution of the cingulate and paracingulate sulcus morphological variants between different diagnostic groups

The purpose was to examine whether the anterior cingulate morphology would be affected by gender and if so, whether this effect would be similar to the one found for the orbitofrontal morphology. In fact, there was a significant difference found in the distribution of the CS pieces in the right hemisphere in female participants (Kruskal - Wallis = 4.512, df = 1, p = 0.034) unlike in males (Kruskal - Wallis = 0.747, df = 2, p = 0.688) with healthy individuals having CS mostly as one piece while patients with schizophrenia possess mostly disconnected CS in the right hemisphere.

Despite absence of any between group differences of the paracingulate morphology in the right hemisphere it was important to examine whether

there is any gender effect on the distribution of the paracingulate sulcus between the groups in both right and left hemispheres. The direct gender analysis did not reveal any gender effect on the distribution of the PCS either in the right or in the left hemisphere.

Patients with schizophrenia were compared to their unaffected relatives. There was a difference found in the distribution of the CS pieces in the right hemisphere in female participants (Kruskal - Wallis = 4.512, df = 1, p = 0.034) unlike in males (Kruskal - Wallis = 0.747, df = 2, p = 0.688) when patients with schizophrenia were compared to their unaffected relatives having CS mostly as one piece while patients with schizophrenia possess mostly disconnected CS in the right hemisphere. The direct gender analysis revealed that female unaffected relatives of patients with schizophrenia had an increased frequency of the prominent PCS in the left hemisphere compared to its distribution in female patients themselves (Kruskal - Wallis = 3.099, df = 1, p = 0.078) and a reduced frequency of absent PCS in the left hemisphere (Kruskal - Wallis = 3.596, df = 1, p = 0.058). Moreover, there was a significant difference found in distribution of the present PCS in the right hemisphere in male participants with its reduced frequency in patients with schizophrenia compared to their male unaffected relatives (Kruskal - Wallis = 4.545, df = 1, p = 0.033).

Patients with bipolar disorder and a family history of bipolar disorder only were compared to their unaffected relatives. There was a difference found in the distribution of the CS pieces in the right hemisphere in male participants (Kruskal - Wallis = 4.832, df = 1, p = 0.028) unlike in females (Kruskal - Wallis = 0.146, df = 2, p = 0.702) when patients with bipolar disorder were compared to their unaffected relatives the latest having mostly disconnected CS in the right hemisphere. The direct gender analysis revealed that male unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder had a reduced frequency of absent PCS in the left

hemisphere (Kruskal - Wallis = 6.469, df = 1, p = 0.011). Moreover, there was a significant difference found in distribution of the PCS in the left hemisphere in female participants (Kruskal - Wallis = 4.254, df = 1, p = 0.039) with an increased frequency of the PCS absent variant in patients with bipolar disorder (Kruskal - Wallis = 4.992, df = 1, p = 0.025) and a reduced frequency of the PCS prominent variant (Kruskal - Wallis = 3.494, df = 1, p = 0.062) compared to their female unaffected relatives. However, there was no gender effect found on expression of the PCS either in female (Kruskal - Wallis = 0.020, df = 1, p = 0.887) or male (Kruskal - Wallis = 0.743, df = 1, p = 0.389) participants in the right hemisphere.

Patients with bipolar disorder and a family history of both bipolar disorder and schizophrenia were compared to their unaffected relatives. There was no difference found in the distribution of the CS pieces in the right and in the left hemisphere in male and in female participants. There was a significant difference found in the distribution of the PCS in the right hemisphere in male participants (Kruskal - Wallis = 6.202, df = 1, p = 0.013). The direct gender analysis revealed that male unaffected relatives of patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder had a reduced frequency of absent PCS in the right hemisphere (Kruskal - Wallis = 5.914, df = 1, p = 0.015) and an increased frequency of the prominent PCS in the right hemisphere (Kruskal - Wallis = 4.832, df = 1, p = 0.028). Moreover, there was a difference found in distribution of the absent PCS in the left hemisphere in female participants (Kruskal - Wallis = 3.676, df = 1, p = 0.055) with an increased frequency of the PCS absent variant in female patients with bipolar disorder compared to their female unaffected relatives.

Patients with schizophrenia were compared to patients with bipolar disorder and a family history of bipolar disorder only. There was no gender effect found in the distribution of the CS pieces either in the right or in the left hemisphere. There was a significant difference found in the distribution of the

present PCS variant in the left hemisphere in male participants (Kruskal - Wallis = 4.220, df = 1, p = 0.040) in such a way that male patients with schizophrenia had an increased frequency of the present PCS in the left hemisphere compared to patients with bipolar disorder.

Patients with schizophrenia were compared to patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder. There was no gender effect found in the distribution of the CS pieces either in the right or in the left hemisphere.

There was a significant difference found in the distribution of the present PCS variant in the left hemisphere in male participants (Kruskal - Wallis = 4.220, df = 1, p = 0.040) in such a way that male patients with schizophrenia had an increased frequency of the present PCS in the left hemisphere compared to patients with bipolar disorder.

Patients with bipolar disorder and a family history of bipolar disorder only were compared to patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder. There was a gender effect found in the distribution of the CS pieces in the right (Kruskal - Wallis = 3.132, df = 1, p = 0.077), but not in the left hemisphere (Kruskal - Wallis = 0.549, df = 1, p = 0.459) in such a way that female patients with bipolar disorder and a family history of bipolar disorder only had an increased frequency of the connected CS (presented as one piece) (Kruskal - Wallis = 3.589, df = 1, p = 0.058) while female patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder had an increased frequency of the disconnected CS (presented in many pieces) (Kruskal - Wallis = 3.589, df = 1, p = 0.058). There was a difference found in the distribution of the PCS variants in the right hemisphere in female participants (Kruskal - Wallis = 3.283, df = 1, p = 0.070) in such a way that female patients with bipolar disorder and a family history of bipolar disorder only had an increased

frequency of the absent PCS variant in the right hemisphere (Kruskal - Wallis = 2.819, df = 1, p = 0.093) and a reduced frequency of the prominent PCS variant (Kruskal - Wallis = 2.887, df = 1, p = 0.089) compared to patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder.

Healthy individuals were compared to unaffected relatives of patients with schizophrenia. There was a gender effect found in the distribution of the CS pieces in the right (Kruskal - Wallis = 5.652, df = 1, p = 0.017), but not in the left hemisphere (Kruskal - Wallis = 0.021, df = 1, p = 0.886) in such a way that female healthy individuals had an increased frequency of the connected CS (presented as one piece) (Kruskal - Wallis = 5.969, df = 1, p = 0.015) while female unaffected relatives of patients with schizophrenia were more likely to have an increased frequency of the disconnected CS (presented in many pieces) in the right hemisphere (Kruskal - Wallis = 5.969, df = 1, p = 0.015). There was a trend to significance found in the distribution of the PCS variants in the left hemisphere in female participants (Kruskal - Wallis = 2.753, df = 1, p = 0.097) in such a way that female unaffected relatives of patients with schizophrenia were more likely to have an increased frequency of the prominent PCS variant in the left hemisphere and a reduced frequency of the absent PCS variant compared female healthy individuals.

Healthy individuals were compared to unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder only. There was no gender effect found in the distribution of the CS pieces either in the right (Kruskal - Wallis = 0.901, df = 1, p = 0.343) or in the left hemisphere (Kruskal - Wallis = 2.003, df = 1, p = 0.157) when female healthy individuals and unaffected relatives of patients with bipolar disorder were compared. However, there was a trend found in the distribution of the CS pieces in the right hemisphere in male individuals (Kruskal - Wallis = 2.893, df = 1, p = 0.089) in such a way that male healthy individuals were more likely to

possess an increased frequency of the disconnected CS (presented in many pieces) (Kruskal - Wallis = 2.848, df = 1, p = 0.091) while male unaffected relatives of patients with bipolar disorder were more likely to have an increased frequency of the connected CS (presented as one piece) in the right hemisphere (Kruskal - Wallis = 2.848, df = 1, p = 0.091).

There was a significant difference found in the distribution of the PCS variants in the left hemisphere in female (Kruskal - Wallis = 4.076, df = 1, p = 0.044) and male (Kruskal - Wallis = 5.323, df = 1, p = 0.021) participants in such a way that unaffected relatives of patients with bipolar disorder were more likely to have an increased frequency of the prominent PCS variant in the left hemisphere (Kruskal - Wallis = 3.604, df = 1, p = 0.058 for females and Kruskal - Wallis = 4.269, df = 1, p = 0.039 for males) and a reduced frequency of the absent PCS variant (Kruskal - Wallis = 3.397, df = 1, p = 0.065 for females and Kruskal - Wallis = 5.081, df = 1, p = 0.024 for males) compared female and male healthy individuals.

Healthy individuals were compared to unaffected relatives of patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder. There was a gender effect found in the distribution of the CS pieces in the right (Kruskal - Wallis = 5.543, df = 1, p = 0.019) and in the left hemisphere (Kruskal - Wallis = 3.243, df = 1, p = 0.072) when female healthy individuals and female unaffected relatives of patients with bipolar disorder were compared in such a way that female unaffected relatives of patients with bipolar disorder were more likely to possess the disconnected CS variant in the right (Kruskal - Wallis = 5.831, df = 1, p = 0.016) and in the left (Kruskal - Wallis = 3.472, df = 1, p = 0.062) hemisphere while female healthy individuals had a prevalence of the connected CS variant in the right (Kruskal - Wallis = 5.831, df = 1, p = 0.016) and in the left (Kruskal - Wallis = 3.472, df = 1, p = 0.062) hemispheres. There was no gender effect found in the distribution of the PCS variants either in the left or in the right hemispheres.

3.5.9 The symmetry - asymmetry comparison of the cingulate and paracingulate sulcul morphological variants between the groups

For assessing symmetry of the cingulate sulcus morphology scans were rated as symmetric if they had the same variant of the cingulate sulcus (a single piece only or 'broken' into segments only) in the right and in the left hemispheres. All the other scans were classified as asymmetric.

With both males and females included there was no group differences found in the symmetry scores either for the CS (Kruskal - Wallis = 2.880, df = 6, p = 0.824) or for PCS (Kruskal - Wallis = 1.930, df = 6, p = 0.824). Although this difference did not reach significant level it is important to notice that healthy individuals tended to be more symmetric in both CS and PCS morphology compared to all patient groups and their unaffected relatives with the biggest difference between healthy controls and patients with schizophrenia. Importantly, the patient groups were less symmetric when compared to their unaffected relatives. When males and females were examined separately, there was a trend found in the CS symmetry scores in the female participants (Kruskal - Wallis = 11.434, df = 6, p = 0.076), but not in males (Kruskal - Wallis = 5.382, df = 6, p = 0.496). The following direct group by group comparison revealed the difference in the CS symmetry scores between female patients with schizophrenia and female patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder (Kruskal - Wallis = 2.819, df = 1, p = 0.093), between female healthy controls and female unaffected relatives of patients with schizophrenia (Kruskal - Wallis = 6.486, df = 1, p = 0.011), female healthy controls and female unaffected relatives of patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder (Kruskal - Wallis = 3.472, df = 1, p = 0.062), and female patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder and their female unaffected relatives (Kruskal - Wallis = 3.333, df = 1, p = 0.068). As in the case of the

orbitofrontal symmetry - asymmetry, healthy controls tended to be more symmetric (of symmetric scans), whereas patients with schizophrenia were more likely to be asymmetric (of symmetric scans).

In order to examine the PCS symmetry scans were rated as symmetric if they possessed the same variant of the paracingulate sulcus (absent, present or prominent) in the right and in the left hemisphere. All the other scans were classified as asymmetric. There was no difference found in the PCS symmetry - asymmetry score either with both males and females included (Kruskal - Wallis = 1.930, df = 6, p = 0.926), or for females (Kruskal - Wallis = 2.255, df = 6, p = 0.895) or males (Kruskal - Wallis = 2.007, df = 6, p = 0.919) separately between all the groups.

3.5.10 Summary

Patients with schizophrenia or bipolar disorder did not vary from healthy individuals in distribution of the cingulate or paracingulate sulcus. However, patients with schizophrenia and bipolar disorder differed from their unaffected relatives in the distribution of the prominent paracingulate sulcus variant in the left hemisphere with an increased frequency of the left prominent paracingulate sulcus in unaffected relatives (38.5% in patients with schizophrenia and 66.7% in their unaffected relatives; 46.2% in patients with bipolar disorder and 81.0% in their unaffected relatives). These findings were replicated in both high risk studies (for details in the Edinburgh High Risk Study see **Chapter 4**; for details in the Bipolar Family Study see **Chapter 5**). This suggests that the paracingulate sulcus could be potential marker to distinguish those at high risk who will or will not develop an illness.

Further, there was a gender effect found on the prevalence of the prominent PCS as the female unaffected relatives of patients with schizophrenia had an increased frequency of the prominent paracingulate sulcus variant in the left

hemisphere compared to its distribution in female patients themselves. In contrary, female patients with bipolar disorder had an increased frequency of the PCS absent variant and a reduced frequency of the PCS prominent variant compared to their female unaffected relatives. Similar differences were correct for male individuals in the right hemisphere.

There was a gender effect found on the distribution of the cingulate sulcus. Female healthy individuals had an increased frequency of the connected CS (presented as one piece) while female unaffected relatives of patients with schizophrenia were more likely to have an increased frequency of the disconnected CS (presented in many pieces) in the right hemisphere. The further issue was the fact that the cingulate sulcus did not share a gender effect with the paracingulate and orbital sulci. The distribution of the cingulate pieces in the right hemisphere were more likely to be associated with female participants while the distribution of the orbitofrontal patterns and the paracingulate sulcus in the right hemisphere were more likely to be associated with males individuals.

Furthermore, healthy individuals tended to be more symmetric in both CS and PCS morphology compared to all patient groups and their unaffected relatives with the biggest difference between healthy controls and patients with schizophrenia. Importantly, the patient groups were less symmetric when compared to their unaffected relatives.

Apart the symmetry – asymmetry issue there is a subject of continuity of orbital or cingulate sulci when healthy individuals were more likely to have a single continuous cingulate sulcus in both hemispheres, while patients with schizophrenia and unaffected relatives of patients with bipolar disorder tend to have a ‘disconnected’ (‘broken’) cingulate sulcus with 2 or 3 pieces (segments). The unaffected relatives of patients with schizophrenia were

more likely to have the cingulate sulcus as one piece while patients with schizophrenia had mostly disconnected CS in the right hemisphere.

3.5.11 Associations between orbitofrontal and anterior cingulate morphology

Healthy controls

With both males and females included, there was a significant association found between the orbitofrontal type II pattern in the left hemisphere and the right cingulate sulcus (Kruskal - Wallis = 6.737, df = 1, p = 0.009) in such a way that those healthy individuals with type II in the left hemisphere were more likely to be in a possession of the connected cingulate sulcus in the right hemisphere compared to those participants that were without the orbitofrontal type II in the left hemisphere.

With both males and females included, there was a significant association between the orbitofrontal patterns in the left hemisphere and the left cingulate sulcus (Kruskal - Wallis = 5.541, df = 1, p = 0.019) in such a way that those healthy individuals with the orbitofrontal type I in the left hemisphere were more likely to be in a possession of the connected cingulate sulcus in the left hemisphere (Kruskal - Wallis = 4.765, df = 1, p = 0.029) while those healthy individuals with the orbitofrontal type III in the left hemisphere were more likely to be in a possession of the disconnected cingulate sulcus in the left hemisphere (Kruskal - Wallis = 3.196, df = 1, p = 0.074) compared to those participants that were without the orbitofrontal type I or without the orbitofrontal type III in the left hemisphere respectively.

There was a significant association found between the orbitofrontal type III in the left hemisphere and the absent paracingulate sulcus variant in the right hemisphere (Kruskal - Wallis = 6.187, df = 1, p = 0.013) in such a way that

those healthy individuals with the orbitofrontal type III in the left hemisphere will more likely to possess the right absent PCS variant compared to those controls without the left orbitofrontal type III.

There was a trend found between the orbitofrontal type I in the left hemisphere and the present paracingulate sulcus variant in the right hemisphere (Kruskal - Wallis = 2.798, df = 1, p = 0.094) in such a way that those healthy individuals with the orbitofrontal type I in the left hemisphere will more likely to possess the right present PCS variant compared to those controls without the left orbitofrontal type I.

There was a significant association found between the orbitofrontal type II in the left hemisphere and the prominent paracingulate sulcus variant in the right hemisphere (Kruskal - Wallis = 4.530, df = 1, p = 0.033) and a trend between the orbitofrontal type III in the left hemisphere and the prominent paracingulate sulcus variant in the right hemisphere (Kruskal - Wallis = 3.109, df = 1, p = 0.078) in such a way that those healthy individuals with the orbitofrontal type II in the left hemisphere and those without the orbitofrontal type III in the left hemisphere will more likely to possess the right prominent PCS variant compared to those controls without the orbitofrontal type II or with the orbitofrontal type III in he left hemisphere.

There was a significant association found between the orbitofrontal type II in the right hemisphere and the present paracingulate sulcus variant in the left hemisphere (Kruskal - Wallis = 5.049, df = 1, p = 0.025) in such a way that those healthy individuals with the orbitofrontal type II in the right hemisphere will more likely to possess the left present PCS variant compared to those controls without the left orbitofrontal type II.

Patients with schizophrenia

With both males and females included, there was a significant association found between the orbitofrontal patterns in the left hemisphere and the right cingulate sulcus (Kruskal - Wallis = 5.068, df = 1, p = 0.024) in such a way that those schizophrenia patients with the orbitofrontal type I in the left hemisphere were more likely to be in a possession of the connected cingulate sulcus in the right hemisphere (Kruskal - Wallis = 4.085, df = 1, p = 0.043) compared to those patients with schizophrenia that were without the orbitofrontal type I in the left hemisphere.

There was a significant association found between the orbitofrontal type II in the left hemisphere and the prominent paracingulate sulcus variant in the left hemisphere (Kruskal - Wallis = 4.229, df = 1, p = 0.040) and between the orbitofrontal type II in the right hemisphere and the prominent paracingulate sulcus variant in the left hemisphere (Kruskal - Wallis = 4.688, df = 1, p = 0.030) in such a way that those schizophrenia patients with the orbitofrontal type II in the left hemisphere and those without the orbitofrontal type II in the right hemisphere will more likely to possess the left prominent PCS variant compared to those schizophrenia patients without the orbitofrontal type II in the left hemisphere or with the orbitofrontal type II in the right hemisphere respectively.

There was a significant association found between the orbitofrontal type II in the left hemisphere and the absent paracingulate sulcus variant in the left hemisphere (Kruskal - Wallis = 6.754, df = 1, p = 0.009) and between the orbitofrontal type II in the right hemisphere and the absent paracingulate sulcus variant in the left hemisphere (Kruskal - Wallis = 5.172, df = 1, p = 0.023) in such a way that those schizophrenia patients with the orbitofrontal type II in the left hemisphere and those without the orbitofrontal type II in the right hemisphere were less likely to possess the left absent PCS variant

compared to those schizophrenia patients without the orbitofrontal type II in the left hemisphere or with the orbitofrontal type II in the right hemisphere respectively.

With both males and females included, there was a significant association found between the orbitofrontal type II in the right hemisphere and the right prominent paracingulate sulcus (Kruskal - Wallis = 4.537, df = 1, p = 0.033) in such a way that those schizophrenia patients with the orbitofrontal type II in the right hemisphere were more likely to be in a possession of the prominent paracingulate sulcus in the right hemisphere compared to those patients with schizophrenia that were without the orbitofrontal type II in the right hemisphere.

With both males and females included, there was a significant association found between the orbitofrontal type II in the right hemisphere and the right absent paracingulate sulcus (Kruskal - Wallis = 6.380, df = 1, p = 0.012) in such a way that those schizophrenia patients with the orbitofrontal type II in the right hemisphere were less likely to be in a possession of the absent paracingulate sulcus variant in the right hemisphere compared to those patients with schizophrenia that were without the orbitofrontal type II in the right hemisphere.

Unaffected relatives of patients with schizophrenia

With both males and females included, there was a significant association found between the orbitofrontal patterns in the right hemisphere and the right absent paracingulate sulcus (Kruskal - Wallis = 6.533, df = 1, p = 0.011) in such a way that those unaffected relatives of schizophrenia patients with the orbitofrontal type I or/and without type III in the right hemisphere were less likely to have the paracingulate sulcus being absent in the right hemisphere (Kruskal - Wallis = 5.914, df = 1, p = 0.015 for type I and Kruskal - Wallis =

3.286, df = 1, p = 0.070 for type III) compared to those unaffected relatives of patients with schizophrenia that were without the orbitofrontal type I or with the orbitofrontal type III in the right hemisphere.

Patients with bipolar disorder and a family history of bipolar disorder only

With both males and females included, there was a significant association found between the orbitofrontal type II in the right hemisphere and the right connected cingulate sulcus (Kruskal - Wallis = 6.370, df = 1, p = 0.012) in such a way that those bipolar patients with the orbitofrontal type II in the right hemisphere were less likely to have the connected cingulate sulcus in the right hemisphere compared to those patients with bipolar disorder that were without the orbitofrontal type II in the right hemisphere.

With both males and females included, there was a significant association found between the orbitofrontal patterns in the right hemisphere and the right prominent paracingulate sulcus (Kruskal - Wallis = 5.083, df = 1, p = 0.024) in such a way that those bipolar patients with the orbitofrontal type III in the right hemisphere were more likely to have the prominent paracingulate sulcus in the right hemisphere (Kruskal - Wallis = 4.275, df = 1, p = 0.039) compared to those patients with bipolar disorder that were without the orbitofrontal type III in the right hemisphere. There was also an association found between the orbitofrontal type III in the left hemisphere and the right prominent PCS (Kruskal - Wallis = 5.515, df = 1, p = 0.019) in such a way that those bipolar patients with the orbitofrontal type III in the left hemisphere were more likely to have the prominent paracingulate sulcus in the right hemisphere compared to those patients with bipolar disorder that were without the orbitofrontal type III in the left hemisphere.

With both males and females included, there was a significant association found between the orbitofrontal type II in the right hemisphere and the right present paracingulate sulcus (Kruskal - Wallis = 4.724, df = 1, p = 0.030) in such a way that those bipolar patients with the orbitofrontal type II in the right hemisphere were more likely to have the present PCS in the right hemisphere compared to those patients with bipolar disorder that were without the orbitofrontal type II in the right hemisphere.

With both males and females included, there was a significant association found between the orbitofrontal patterns in the right hemisphere and the right absent paracingulate sulcus (Kruskal - Wallis = 7.006, df = 1, p = 0.008) in such a way that those bipolar patients with the orbitofrontal type I and/or without the orbitofrontal type III in the right hemisphere were more likely to have the absent paracingulate sulcus in the right hemisphere (Kruskal - Wallis = 8.218, df = 1, p = 0.004 for type I and Kruskal - Wallis = 4.229, df = 1, p = 0.040) compared to those patients with bipolar disorder that were without the orbitofrontal type I or with the orbitofrontal type III in the right hemisphere. There was also an association found between the orbitofrontal types II and III in the left hemisphere and the right absent PCS (Kruskal - Wallis = 5.757, df = 1, p = 0.016 for type II and Kruskal - Wallis = 8.644, df = 1, p = 0.003) in such a way that those bipolar patients with the orbitofrontal type II and without the orbitofrontal type III in the left hemisphere were more likely to have the absent paracingulate sulcus in the right hemisphere compared to those patients with bipolar disorder that were without the orbitofrontal type II and/or with the orbitofrontal type III in the left hemisphere.

Unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder only

With both males and females included, there was a significant association found between the orbitofrontal patterns in the right hemisphere and the

connected cingulate sulcus in the left hemisphere (Kruskal - Wallis = 8.084, df = 1, p = 0.004) in such a way that those unaffected relatives of bipolar patients with the orbitofrontal type I and/or without the orbitofrontal type III in the right hemisphere were more likely to have the connected cingulate sulcus in the left hemisphere (Kruskal - Wallis = 7.108, df = 1, p = 0.008 for type I and Kruskal - Wallis = 3.421, df = 1, p = 0.064 for type III) compared to those unaffected relatives of patients with bipolar disorder that were without the orbitofrontal type I or with the orbitofrontal type III in the right hemisphere.

With both males and females included, there was a significant association found between the orbitofrontal patterns in the left hemisphere and the connected cingulate sulcus in the right hemisphere (Kruskal - Wallis = 4.753, df = 1, p = 0.029) in such a way that those unaffected relatives of bipolar patients with the orbitofrontal type I and/or without the orbitofrontal type III in the left hemisphere were more likely to have the connected cingulate sulcus in the right hemisphere (Kruskal - Wallis = 3.030, df = 1, p = 0.082 for type I and Kruskal - Wallis = 4.902, df = 1, p = 0.027 for type III) compared to those unaffected relatives of patients with bipolar disorder that were without the orbitofrontal type I or with the orbitofrontal type III in the left hemisphere.

With both males and females included, there was a significant association found between the orbitofrontal type III in the left hemisphere and the absent paracingulate sulcus in the left hemisphere (Kruskal - Wallis = 4.250, df = 1, p = 0.039) in such a way that those unaffected relatives of bipolar patients with the orbitofrontal type III in the left hemisphere were more likely to have the absent paracingulate sulcus in the left hemisphere compared to those unaffected relatives of patients with bipolar disorder that were without the orbitofrontal type III in the left hemisphere.

Patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder

With both males and females included, there was a significant association found between the orbitofrontal patterns in the right hemisphere and the connected cingulate sulcus in the right hemisphere (Kruskal - Wallis = 3.420, df = 1, p = 0.064) in such a way that those bipolar patients with the orbitofrontal type I and/or without the orbitofrontal type II in the right hemisphere were more likely to have the connected cingulate sulcus in the right hemisphere (Kruskal - Wallis = 6.009, df = 1, p = 0.014 for type I and Kruskal - Wallis = 5.786, df = 1, p = 0.016 for type II) compared to those patients with bipolar disorder that were without the orbitofrontal type I or with the orbitofrontal type II in the right hemisphere.

Unaffected relatives of patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder

With both males and females included, there was a significant association found between the orbitofrontal type III in the right hemisphere and the present paracingulate sulcus in the left hemisphere (Kruskal - Wallis = 6.588, df = 1, p = 0.010) in such a way that those unaffected relatives of bipolar patients with the orbitofrontal type III in the right hemisphere were more likely to have the present paracingulate sulcus in the left hemisphere compared to those unaffected relatives of patients with bipolar disorder that were without the orbitofrontal type III in the right hemisphere.

3.5.12 Association between cingulate and paracingulate sulci

Healthy controls

With both genders combined there was an association found between the left cingulate sulcus and the left present (Kruskal - Wallis = 3.196, df = 1, p = 0.074) paracingulate sulci in healthy controls in such a way that participants with the present PCS variant in the left hemisphere were less likely to posses the connected cingulate sulcus in the left hemisphere. There was no convincing gender effect found on this association although it is possible that this association is more likely to be found in females (Kruskal - Wallis = 5.175, df = 2, p = 0.075), rather than in males (Kruskal - Wallis = 0.133, df = 1, p = 0.715).

Patients with schizophrenia

With both genders combined there was a significant association found between the left cingulate sulcus and the left present (Kruskal - Wallis = 4.339, df = 1, p = 0.037) paracingulate sulcus in patients with schizophrenia in such a way that participants with the present PCS variant in the left hemisphere were less likely to posses the connected cingulate sulcus in the left hemisphere.

Unaffected relatives of patients with schizophrenia

There was not any significant association found between paracingulate and cingulate sulci in either hemisphere.

Patients with bipolar disorder and a family history of bipolar disorder only

With both genders combined there was a significant association found between the left cingulate sulcus and the right paracingulate sulcus (Kruskal - Wallis = 7.968, df = 1, p = 0.005) in patients with bipolar disorder in such a way that participants with the present PCS (Kruskal - Wallis = 4.724, df = 1, p = 0.030) and without the absent PCS variant (Kruskal - Wallis = 9.524, df = 1, p = 0.002) in the right hemisphere were less likely to posses the connected cingulate sulcus in the left hemisphere.

Unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder only

With both genders combined there was a significant association found between the right cingulate sulcus and the left absent PCS variant (Kruskal - Wallis = 6.000, df = 1, p = 0.014) in unaffected relatives of patients with bipolar disorder in such a way that participants with the absent PCS variant in the left hemisphere were less likely to posses the connected cingulate sulcus in the right hemisphere.

Patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder

With both genders combined there was a significant association found between the left cingulate sulcus and the right absent (Kruskal - Wallis = 3.704, df = 1, p = 0.054) and present PCS variants (Kruskal - Wallis = 3.630, df = 1, p = 0.057) in patients with bipolar disorder in such a way that participants with the present PCS and without the absent PCS variant in the right hemisphere were less likely to posses the connected cingulate sulcus in the left hemisphere.

Unaffected relatives of patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder

There was not any significant association found between paracingulate and cingulate sulci in either hemisphere.

3.5.13 Summary

There is an indication in this data on the connection between the orbitofrontal and anterior cingulate morphology in the right and left hemispheres. For example, healthy individuals with type II in the left hemisphere were more likely to be in a possession of the connected cingulate sulcus in the right hemisphere compared to those participants that were without the orbitofrontal type II in the left hemisphere. Unaffected relatives of the schizophrenia patients with the orbitofrontal type I or/and without type III in the right hemisphere were less likely to have the paracingulate sulcus being absent in the right hemisphere compared to those unaffected relatives of patients with schizophrenia that were without the orbitofrontal type I or with the orbitofrontal type III in the right hemisphere. Patients with bipolar disorder had the orbitofrontal sulcogyral patterns being associated with the cingulate cortex in the same hemisphere as well as in the opposite one. The bipolar patients with the orbitofrontal type III in the right hemisphere were more likely to have the prominent paracingulate sulcus in the right hemisphere compared to those patients with bipolar disorder that were without the orbitofrontal type III in the right hemisphere. There was also an association found between the orbitofrontal type III in the left hemisphere and the right prominent PCS in such a way that those bipolar patients with the orbitofrontal type III in the left hemisphere were more likely to have the prominent paracingulate sulcus in the right hemisphere compared to those patients with bipolar disorder that were without the orbitofrontal type III in the left hemisphere.

There was an interesting observation made related to the connectivity of the orbitofrontal morphology and the connectivity of the anterior cingulate morphology. For example, healthy individuals with the orbitofrontal type I (half-connected, half-disconnected pattern) in the left hemisphere were more likely to be in a possession of the connected cingulate sulcus in the left hemisphere while those healthy individuals with the orbitofrontal type III (mostly disconnected pattern) in the left hemisphere were more likely to be in a possession of the disconnected cingulate sulcus in the left hemisphere. Even the schizophrenia patients with the orbitofrontal type I in the left hemisphere were more likely to be in a possession of the connected cingulate sulcus in the right hemisphere compared to those patients with schizophrenia that were without the orbitofrontal type I in the left hemisphere. The bipolar patients with the orbitofrontal type I and/or without the orbitofrontal type II in the right hemisphere were more likely to have the connected cingulate sulcus in the right hemisphere compared to those patients with bipolar disorder that were without the orbitofrontal type I or with the orbitofrontal type II in the right hemisphere. Further, unaffected relatives of bipolar patients with the orbitofrontal type I and/or without the orbitofrontal type III in the right hemisphere were more likely to have the connected cingulate sulcus in the left hemisphere compared to those unaffected relatives of patients with bipolar disorder that were without the orbitofrontal type I or with the orbitofrontal type III in the right hemisphere. This suggests that the 'connectivity-connectivity' associations between the orbitofrontal and cingulate morphology may not be diagnosis related but be a characteristic of the orbitofrontal sulcogyral patterns and cingulate sulcus variants themselves.

Associations between cingulate and paracingulate sulcus were found either in the same hemisphere (between the left cingulate sulcus and the left present in patients with schizophrenia), or between the opposite hemispheres (the left cingulate sulcus and the right paracingulate sulcus in patients with

bipolar disorder or the right cingulate sulcus and the left paracingulate sulcus in unaffected relatives of patients with bipolar disorder).

3.5.14 Neuropsychological and clinical associations of orbitofrontal morphology

Neuropsychological and clinical associations of the orbitofrontal pattern morphological variants were examined in the healthy controls, patients with schizophrenia, bipolar disorder and their unaffected relatives. Furthermore, it was investigated whether orbitofrontal morphology on its own or in combination with the anterior cingulate morphological variants might distinguish patients with schizophrenia or bipolar disorder from their unaffected relatives.

3.5.14.1 The orbitofrontal morphology and IQ

Healthy Controls

With both males and females included the orbitofrontal type I in the right hemisphere was found to be associated with the NART score (Kruskal - Wallis = 4.108, df = 1, p = 0.043) and full scale IQ (Kruskal - Wallis = 4.108, df = 1, p = 0.043) arriving from the verbal IQ score (Kruskal - Wallis = 4.019, df = 1, p = 0.045) in such a way that healthy individuals with type I in the right hemisphere scored higher compared to those participants who were without type I in the right hemisphere.

With both males and females included the orbitofrontal type II in the right hemisphere was found to be associated with the WASI full scale (Kruskal - Wallis = 4.779, df = 1, p = 0.029) including the WASI verbal IQ (Kruskal - Wallis = 4.508, df = 1, p = 0.034), WASI performance IQ (Kruskal - Wallis = 3.700, df = 1, p = 0.054), WASI vocabulary score (Kruskal - Wallis = 4.947, df

= 1, p = 0.026), WASI block design score (Kruskal -Wallis = 4.257, df = 1, p = 0.039) and WASI similarities score (Kruskal - Wallis = 3.066, df = 1, p = 0.080) in such a way that healthy individuals with type II in the right hemisphere scored higher compared to those participants who were without type II in the right hemisphere.

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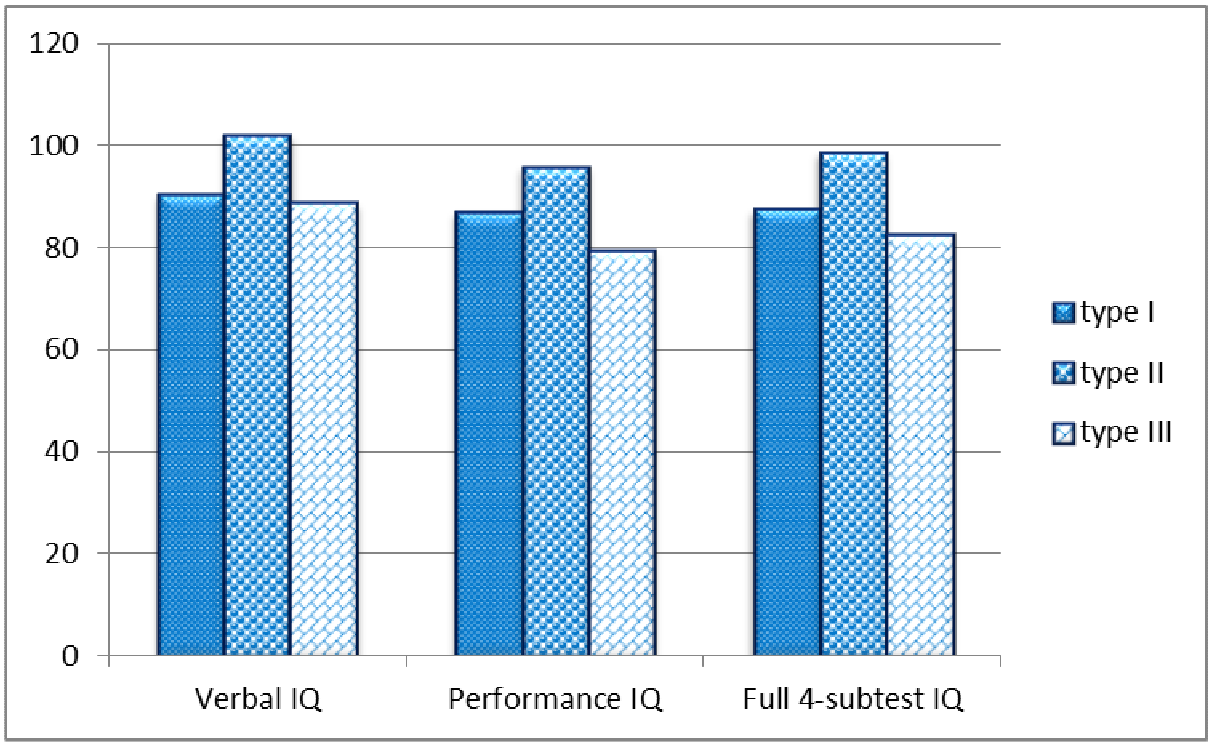
With both males and females included the orbitofrontal type II in the left hemisphere was found to be associated with the NART score (Kruskal - Wallis = 3.577, df = 1, p = 0.059) and full scale IQ (Kruskal - Wallis = 3.577, df = 1, p = 0.059) in such a way that healthy individuals with type II in the left hemisphere scored higher compared to those participants who were without type II in the left hemisphere.

Patients with schizophrenia

With both males and females included the orbitofrontal type II in the right hemisphere was found to be associated with the NART score (Kruskal - Wallis = 3.560, df = 1, p = 0.059) and full scale IQ (Kruskal - Wallis = 7.338, df = 1, p = 0.0507) including WASI vocabulary score (Kruskal - Wallis = 4.561, df = 1, p = 0.033), WASI block design score (Kruskal - Wallis = 3.784, df = 1, p = 0.052), WASI performance (Kruskal - Wallis = 4.152, df = 1, p = 0.042) and WASI verbal IQ (Kruskal - Wallis = 3.418, df = 1, p = 0.064) in such a way that patients with schizophrenia with type II in the right hemisphere scored higher compared to those participants who were without type II in the right hemisphere (See **Figure 3.13**).

With both males and females included the orbitofrontal type III in the right hemisphere was found to be associated with the WASI block design score (Kruskal - Wallis = 5.054, df = 1, p = 0.025) in such a way that the schizophrenia patients with type III in the right hemisphere scored less than patients with any other orbitofrontal pattern (See **Figure 3.13**).

Figure 3.13. The WASI IQ scores in patients with schizophrenia with orbitofrontal types I, II and III in the right hemisphere, the Psychosis Study. This bar chart demonstrates the mean measures of full scale (Full 4-subtest), performance and verbal IQ.



With both males and females included the orbitofrontal type II in the left hemisphere was found to be associated with the WASI performance IQ (Kruskal - Wallis = 3.526, df = 1, p = 0.060) and WASI matrix reasoning score (Kruskal - Wallis = 4.243, df = 1, p = 0.039) in such a way that the schizophrenia patients with type II in the left hemisphere scored higher than patients with any other type.

Unaffected relatives of patients with schizophrenia

With both males and females included the orbitofrontal type I in the right hemisphere was found to be associated with the WASI verbal IQ (Kruskal - Wallis = 2.722, df = 1, p = 0.099) and WASI similarities scores (Kruskal - Wallis = 5.212, df = 1, p = 0.022) in such a way that participants with type I in the right hemisphere scored higher than those with any other orbitofrontal pattern.

With both males and females included the orbitofrontal type III in the left hemisphere was found to be associated with the WASI performance IQ (Kruskal - Wallis = 2.871, df = 1, p = 0.090) and WASI block design score (Kruskal - Wallis = 2.934, df = 1, p = 0.087) in such a way that participants with type III in the left hemisphere scored less than those with any other orbitofrontal pattern.

Patients with bipolar disorder and a family history of bipolar disorder only

There was no association found between the orbitofrontal morphology and IQ scores in this particular group.

Unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder only

With both males and females included the orbitofrontal type III in the right hemisphere was found to be associated with the WASI block design score (Kruskal - Wallis = 4.001, df = 1, p = 0.045) and WASI similarities score (Kruskal - Wallis = 3.581, df = 1, p = 0.058) in such a way that the participants with type III in the right hemisphere scored less than those with any other orbitofrontal pattern.

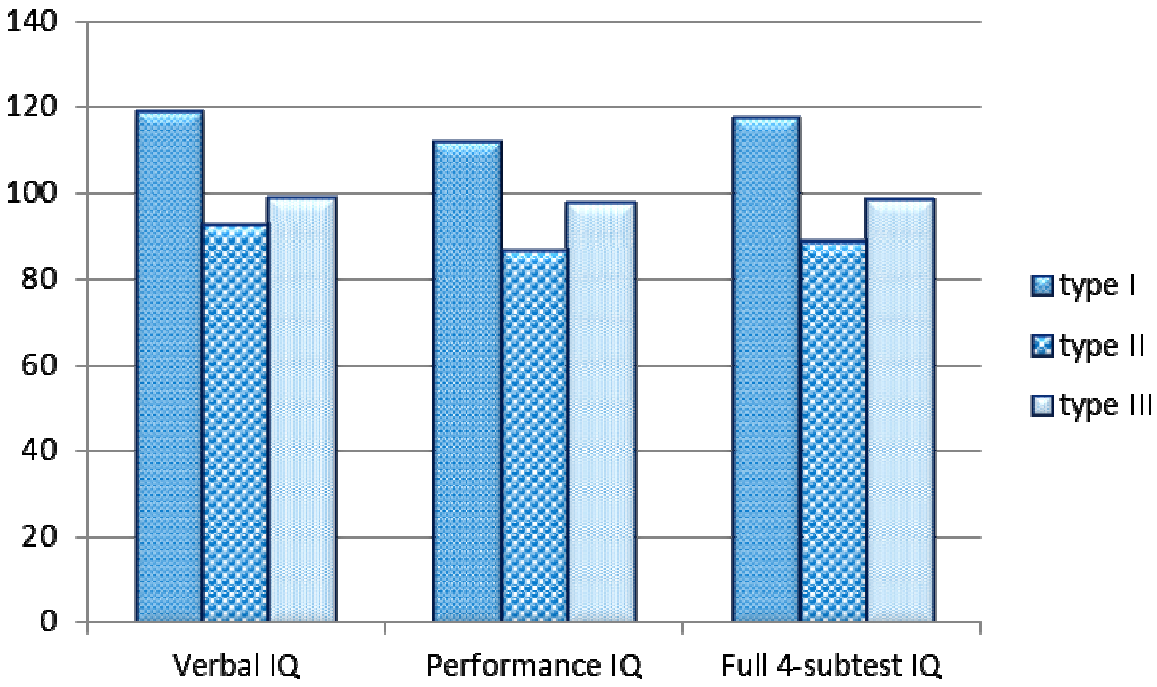
With both males and females included the orbitofrontal type II in the left hemisphere was found to be associated with the WASI performance IQ (Kruskal - Wallis = 3.493, df = 1, p = 0.062) in such a way that the participants with type II in the left hemisphere scored higher than those with any other orbitofrontal pattern.

Patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder

With both males and females included the orbitofrontal type I in the left hemisphere was found to be associated with the NART score (Kruskal - Wallis = 5.812, df = 1, p = 0.016) and full scale IQ (Kruskal - Wallis = 8.301, df = 1, p = 0.004) including WASI verbal IQ (Kruskal - Wallis = 9.265, df = 1, p = 0.002), WASI performance IQ (Kruskal - Wallis = 7.792, df = 1, p = 0.005), WASI vocabulary score (Kruskal - Wallis = 10.089, df = 1, p = 0.001), WASI block design score (Kruskal - Wallis = 6.882, df = 1, p = 0.009), WASI similarities score (Kruskal - Wallis = 6.249, df = 1, p = 0.012) and WASI matrix reasoning score (Kruskal - Wallis = 3.012, df = 1, p = 0.083) in such a way that patients with bipolar disorder with type I in the left hemisphere scored higher compared to those participants who were without type I in the left hemisphere (See **Figure 3.14** for details).

With both males and females included the orbitofrontal type I in the right hemisphere was found to be associated with the WASI similarities score (Kruskal - Wallis = 3.860, df = 1, p = 0.049) in such a way that the bipolar disorder patients with type I in the right hemisphere scored higher than patients with any other orbitofrontal pattern.

Figure 3.14. The WASI IQ scores in patients with bipolar disorder and a family history of both bipolar disorder and schizophrenia, the Psychosis Study. This bar chart demonstrates the mean measures of full scale (Full 4-subtest), performance and verbal IQ for the orbitofrontal patterns (types I, II and III) in the left hemisphere.



With both males and females included the orbitofrontal type II in the left hemisphere was found to be associated with the WASI full scale IQ (Kruskal - Wallis = 6.503, df = 1, p = 0.011), WASI verbal IQ (Kruskal - Wallis = 4.435, df = 1, p = 0.035), WASI performance IQ (Kruskal - Wallis = 8.392, df = 1, p = 0.004), WASI vocabulary score (Kruskal - Wallis = 5.843, df = 1, p = 0.016), WASI block design score (Kruskal - Wallis = 8.655, df = 1, p = 0.003) and WASI similarities score (Kruskal - Wallis = 3.410, df = 1, p = 0.065) in such a way that the bipolar disorder patients with type II in the left hemisphere scored less than patients with any other orbitofrontal pattern (See **Figure 3.14** for details).

Unaffected relatives of patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder

With both males and females included the orbitofrontal type II in the right hemisphere was found to be associated with the WASI performance IQ (Kruskal - Wallis = 3.016, df = 1, p = 0.082), the WASI block design score (Kruskal - Wallis = 2.917, df = 1, p = 0.088) and WASI matrix reasoning score (Kruskal - Wallis = 3.329, df = 1, p = 0.068) in such a way that the participants with type II in the right hemisphere scored less than those with any other orbitofrontal pattern.

With both males and females included the orbitofrontal type III in the right hemisphere was found to be associated with the WASI full score (Kruskal - Wallis = 3.121, df = 1, p = 0.077) developing from WASI verbal IQ (Kruskal - Wallis = 5.060, df = 1, p = 0.024) and WASI vocabulary score (Kruskal - Wallis = 3.888, df = 1, p = 0.049) and WASI similarities score (Kruskal - Wallis = 5.451, df = 1, p = 0.020) in such a way that the participants with type III in the right hemisphere scored higher than those with any other orbitofrontal pattern.

With both males and females included the orbitofrontal type I in the left hemisphere was found to be associated with the NART score (Kruskal - Wallis = 3.719, df = 1, p = 0.054) and full scale IQ (Kruskal - Wallis = 3.719, df = 1, p = 0.054) including WASI verbal IQ (Kruskal - Wallis = 4.873, df = 1, p = 0.027), WASI vocabulary score (Kruskal - Wallis = 5.595, df = 1, p = 0.018) and WASI similarities score (Kruskal - Wallis = 3.335, df = 1, p = 0.068) in such a way that unaffected relatives of patients with bipolar disorder with type I in the left hemisphere scored higher compared to those participants who were without type I in the left hemisphere.

With both males and females included the orbitofrontal type II in the left hemisphere was found to be associated with the WASI block design score (Kruskal-Wallis = 5.230, df = 1, p = 0.022) in such a way that unaffected relatives of patients with bipolar disorder with type II in the left hemisphere scored less than those with any other orbitofrontal pattern.

With both males and females included the orbitofrontal type III in the left hemisphere was found to be associated with the WASI verbal IQ (Kruskal-Wallis = 4.760, df = 1, p = 0.029) and WASI vocabulary score (Kruskal-Wallis = 4.776, df = 1, p = 0.029) in such a way that unaffected relatives of patients with bipolar disorder with type III in the left hemisphere scored less than those with any other orbitofrontal pattern.

3.5.14.2 The Rivermead Memory Test and the orbitofrontal morphology

Healthy Controls

With both males and females included the orbitofrontal type III in the left hemisphere was found to be associated with the face recognition profile score (Kruskal - Wallis = 5.442, df = 1, p = 0.020) in such a way that healthy individuals with type III in the left hemisphere scored higher compared to those participants who were without type III in the left hemisphere.

Patients with schizophrenia

With both males and females included the orbitofrontal type III in the right hemisphere was found to be associated with the story immediate profile score (Kruskal - Wallis = 7.517, df = 1, p = 0.006) and with the story delayed profile score (Kruskal - Wallis = 3.455, df = 1, p = 0.063) in such a way that patients with schizophrenia with type III in the right hemisphere scored higher

compared to those participants who were without type III in the right hemisphere.

With both males and females included the orbitofrontal type III in the left hemisphere was found to be associated with the total profile score (Kruskal - Wallis = 5.698, df = 1, p = 0.017) in such a way that patients with schizophrenia with type III in the left hemisphere scored higher compared to those participants who were without type III in the left hemisphere.

Unaffected relatives of patients with schizophrenia

With both males and females included the orbitofrontal type III in the right hemisphere was found to be associated with the face recognition profile score (Kruskal - Wallis = 5.086, df = 1, p = 0.024) in such a way that unaffected relatives of patients with schizophrenia with type III in the right hemisphere scored higher compared to those participants who were without type III in the right hemisphere.

Patients with bipolar disorder and a family history of bipolar disorder only

With both males and females included the orbitofrontal type I in the left hemisphere was found to be associated with the orientation and date profile score (Kruskal -Wallis = 2.956, df = 1, p = 0.086) in such a way that patients with bipolar disorder with type I in the left hemisphere scored higher compared to those participants who were without type I in the left hemisphere.

With both males and females included the orbitofrontal type II in the right hemisphere was found to be associated with the face recognition profile score (Kruskal - Wallis = 3.395, df = 1, p = 0.065) in such a way that patients

with bipolar disorder with type II in the right hemisphere scored higher compared to those participants who were without type II in the right hemisphere.

Unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder only

With both males and females included the orbitofrontal type III in the right hemisphere was found to be associated with the total profile score (Kruskal - Wallis = 2.843, df = 1, p = 0.092) in such a way that unaffected relatives of patients with bipolar disorder with type III in the right hemisphere scored higher compared to those participants who were without type III in the right hemisphere.

With both males and females included the orbitofrontal type II in the right hemisphere was found to be associated with the story delayed profile score (Kruskal - Wallis = 3.146, df = 1, p = 0.076) and with the total profile score (Kruskal - Wallis = 2.756, df = 1, p = 0.097) in such a way that unaffected relatives of patients with bipolar disorder with type II in the right hemisphere scored higher compared to those participants who were without type II in the right hemisphere.

With both males and females included the orbitofrontal type II in the left hemisphere was found to be associated with the picture recognition profile score (Kruskal - Wallis = 3.078, df = 1, p = 0.079) in such a way that unaffected relatives of patients with bipolar disorder with type II in the left hemisphere scored higher compared to those participants who were without type II in the left hemisphere.

Patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder

With both males and females included the orbitofrontal type III in the right hemisphere was found to be associated with the face recognition profile score (Kruskal - Wallis = 8.803, df = 1, p = 0.003) and with the story delayed profile score (Kruskal - Wallis = 2.779, df = 1, p = 0.095) in such a way that patients with bipolar disorder with type III in the right hemisphere scored higher compared to those participants who were without type III in the right hemisphere.

With both males and females included the orbitofrontal type I in the right hemisphere was found to be associated with the face recognition profile score (Kruskal - Wallis = 5.964, df = 1, p = 0.015) in such a way that patients with bipolar disorder with type I in the right hemisphere scored higher compared to those participants who were without type I in the right hemisphere.

Unaffected relatives of patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder

With both males and females included the orbitofrontal type III in the right hemisphere was found to be associated with the story immediate profile score (Kruskal - Wallis = 3.387, df = 1, p = 0.066) in such a way that unaffected relatives of patients with bipolar disorder with type III in the right hemisphere scored higher compared to those participants who were without type III in the right hemisphere. With both males and females included the orbitofrontal type II in the right hemisphere was found to be associated with the story immediate profile score (Kruskal - Wallis = 4.640, df = 1, p = 0.031) and with the story delayed profile score (Kruskal - Wallis = 4.839, df = 1, p = 0.028) in such a way that unaffected relatives of patients with bipolar disorder

with type II in the right hemisphere scored higher compared to those participants who were without type II in the right hemisphere.

With both males and females included the orbitofrontal type II in the left hemisphere was found to be associated with the total profile score (Kruskal - Wallis = 3.722, df = 1, p = 0.054) in such a way that unaffected relatives of patients with bipolar disorder with type II in the left hemisphere scored higher compared to those participants who were without type II in the left hemisphere.

3.5.14.3 The Hayling Sentence Completion Task

Healthy Controls

With both males and females included the orbitofrontal type II in the right hemisphere was found to be associated with the HSCT converted scaled errors score section 2 (Kruskal - Wallis = 3.002, df = 1, p = 0.083) in such a way that healthy individuals with type II in the right hemisphere scored higher (made more errors) compared to those participants who were without type II in the right hemisphere.

Patients with schizophrenia

With both males and females included the orbitofrontal type II in the right hemisphere was found to be associated with the HSCT total time scaled score (Kruskal - Wallis = 5.314, df = 1, p = 0.021) and with the HSCT converted scaled errors score section 2 (Kruskal - Wallis = 3.551, df = 1, p = 0.060) in such a way that patients with schizophrenia with type II in the right hemisphere scored higher (were slower and made more errors) compared to those participants who were without type II in the right hemisphere.

With both males and females included the orbitofrontal type III in the right hemisphere was found to be associated with the HSCT total time scaled score section 2 (Kruskal - Wallis = 3.324, df = 1, p = 0.068) in such a way that patients with schizophrenia with type III in the right hemisphere scored higher (were slower) compared to those participants who were without type III in the right hemisphere.

With both males and females included the orbitofrontal type I in the left hemisphere was found to be associated with the HSCT total time scaled score section 2 (Kruskal - Wallis = 4.494, df = 1, p = 0.034) in such a way that patients with schizophrenia with type I in the left hemisphere scored higher compared to those participants who were without type I in the left hemisphere.

With both males and females included the orbitofrontal type III in the left hemisphere was found to be associated with the HSCT total time scaled score section 2 (Kruskal - Wallis = 3.259, df = 1, p = 0.071) in such a way that patients with schizophrenia with type III in the left hemisphere scored higher compared to those participants who were without type III in the left hemisphere.

Unaffected relatives of patients with schizophrenia

With both males and females included the orbitofrontal type I in the right hemisphere was found to be associated with the HSCT converted scaled errors score section 2 (Kruskal - Wallis = 3.636, df = 1, p = 0.057) in such a way that unaffected relatives of patients with schizophrenia with type I in the right hemisphere scored higher compared to those participants who were without type I in the right hemisphere.

With both males and females included the orbitofrontal type II in the left hemisphere was found to be associated with the HSCT total time scaled score section 1 (Kruskal - Wallis = 3.082, df = 1, p = 0.079) in such a way that unaffected relatives of patients with schizophrenia with type II in the left hemisphere scored higher (were slower) compared to those participants who were without type II in the left hemisphere.

Patients with bipolar disorder and a family history of bipolar disorder only

There was not any association found between the orbitofrontal patterns and the HSCT scores in this group.

Unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder only

With both males and females included the orbitofrontal type II in the right hemisphere was found to be associated with the HSCT total time scaled score section 2 (Kruskal - Wallis = 3.500, df = 1, p = 0.061) in such a way that unaffected relatives of patients with bipolar disorder with type II in the right hemisphere scored higher compared to those participants who were without type II in the right hemisphere.

With both males and females included the orbitofrontal type I in the left hemisphere was found to be associated with the HSCT converted scaled errors score section 2 (Kruskal - Wallis = 3.725, df = 1, p = 0.054) in such a way that unaffected relatives of patients with bipolar disorder with type I in the left hemisphere scored higher compared to those participants who were without type I in the left hemisphere.

With both males and females included the orbitofrontal type II in the left hemisphere was found to be associated with the HSCT total scaled score (Kruskal - Wallis = 3.196, df = 1, p = 0.074) and with the HSCT converted scaled errors score section 2 (Kruskal - Wallis = 5.201, df = 1, p = 0.023) in such a way that unaffected relatives of patients with bipolar disorder with type II in the left hemisphere scored higher compared to those participants who were without type II in the left hemisphere.

Patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder

With both males and females included the orbitofrontal type I in the left hemisphere was found to be associated with the HSCT total time scaled score section 1 (Kruskal - Wallis = 3.503, df = 1, p = 0.061) in such a way that patients with bipolar disorder with type I in the left hemisphere scored higher compared to those participants who were without type I in the left hemisphere.

With both males and females included the orbitofrontal type II in the left hemisphere was found to be associated with the HSCT total time scaled score section 1 (Kruskal - Wallis = 6.966, df = 1, p = 0.008) in such a way that patients with bipolar disorder with type II in the left hemisphere scored higher (were slower) compared to those participants who were without type II in the left hemisphere.

Unaffected relatives of patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder

With both males and females included the orbitofrontal type I in the right hemisphere was found to be associated with the HSCT total time scaled score section 1 (Kruskal - Wallis = 2.915, df = 1, p = 0.088) in such a way

that unaffected relatives of patients with bipolar disorder with type I in the right hemisphere scored higher compared to those participants who were without type I in the right hemisphere.

With both males and females included the orbitofrontal type III in the right hemisphere was found to be associated with the HSCT total time scaled score section 1 (Kruskal - Wallis = 3.794, df = 1, p = 0.051) in such a way that unaffected relatives of patients with bipolar disorder with type III in the right hemisphere scored higher compared to those participants who were without type III in the right hemisphere.

With both males and females included the orbitofrontal type III in the left hemisphere was found to be associated with the HSCT total time scaled score section 2 (Kruskal - Wallis = 3.968, df = 1, p = 0.046) in such a way that unaffected relatives of patients with bipolar disorder with type III in the left hemisphere scored higher (were slower) compared to those participants who were without type III in the left hemisphere.

3.5.14.4 The Young Mania Rating Scale

Also there was not any significant associations found those with the orbitofrontal type III in either hemisphere scored higher in the Young Mania Rating Scale overall compared to participants with any other type (mean = 2.20 (SD = 3.816) for the orbitofrontal type I, mean = 1.64 (SD = 3.163) for type II, and mean = 3.30 (SD = 6.292) for type III in the right hemisphere).

3.5.14.5 The Hamilton Depression Rating Scale

Healthy Controls

There was not any association found between the orbitofrontal sulcogyral patterns and the HDRS scores in this group.

Patients with schizophrenia

There was not any association found between the orbitofrontal sulcogyral patterns and the HDRS scores in this group.

Unaffected relatives of patients with schizophrenia

With both males and females included the orbitofrontal type I in the right hemisphere was found to be associated with the Hamilton Depression Rating Scale total score (Kruskal - Wallis = 6.452, df = 1, p = 0.011) in such a way that unaffected relatives of patients with schizophrenia with type I in the right hemisphere scored higher compared to those participants who were without type I in the right hemisphere.

With both males and females included the orbitofrontal type III in the right hemisphere was found to be associated with the HDRS total score (Kruskal - Wallis = 4.682, df = 1, p = 0.030) in such a way that unaffected relatives of patients with schizophrenia with type III in the right hemisphere scored higher compared to those participants who were without type III in the right hemisphere.

Patients with bipolar disorder and a family history of bipolar disorder only

With both males and females included the orbitofrontal type III in the left hemisphere was found to be associated with the HDRS total score (Kruskal - Wallis = 6.629, df = 1, p = 0.010) in such a way that patients with bipolar disorder with type III in the left hemisphere scored higher compared to those participants who were without type III in the left hemisphere.

Unaffected relatives of patients with bipolar disorder and a family history of bipolar disorder only

There was not any association found between the orbitofrontal sulcogyral patterns and the HDRS scores in this group.

Patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder

There was not any association found between the orbitofrontal sulcogyral patterns and the HDRS scores in this group.

Unaffected relatives of patients with bipolar disorder and a family history of both schizophrenia and bipolar disorder

With both males and females included the orbitofrontal type II in the left hemisphere was found to be associated with the HDRS total score (Kruskal - Wallis = 3.010, df = 1, p = 0.083) in such a way that unaffected relatives of patients with bipolar disorder with type II in the left hemisphere scored higher compared to those participants who were without type II in the left hemisphere.

With both males and females included the orbitofrontal type III in the left hemisphere was found to be associated with the HDRS total score (Kruskal - Wallis = 3.945, df = 1, p = 0.047) in such a way that unaffected relatives of patients with bipolar disorder with type III in the left hemisphere scored higher compared to those participants who were without type III in the left hemisphere.

3.5.15 Positive and negative predictive values and sensitivity of the orbitofrontal morphology alone and in combination with the paracingulate variants

The positive and negative predictive values were calculated, as well as sensitivity and specificity of those conditions when one or both following structural markers in one subject were identified: the right orbitofrontal sulcogyral pattern type III and/or the left prominent or absent paracingulate variant in patients with schizophrenia and their unaffected relatives, the right and left orbitofrontal sulcogyral pattern type III and/or the left absent paracingulate variant in patients with bipolar disorder and a family history of bipolar disorder only and their unaffected relatives. The orbitofrontal type III in the right and left hemisphere was chosen for this analysis as the distributions of both these markers were found to be altered in participants with schizophrenia and bipolar disorder.

The positive predictive value in this case was proportion of the schizophrenia or bipolar disorder patients with the right orbitofrontal type III and/or the left prominent/absent PCS, and also the left orbitofrontal type III and/or the right absent PCS in patients with bipolar affective disorder.

The negative predictive value was proportion of those unaffected relatives of patients with schizophrenia without type III in the right hemisphere and/or the left prominent/absent PCS compared to patients with schizophrenia.

Likewise, the negative predictive value was proportion of unaffected relatives of patients with bipolar disorder without type III in the right or left hemisphere and/or the right or left absent PCS compared to patients with bipolar disorder. Sensitivity in this case was the probability that presence of the right (or left) orbitofrontal type III and/or the right or left prominent/absent PCS will indicate schizophrenia (bipolar disorder) among those with schizophrenia (bipolar disorder) and their unaffected relatives.

Specificity was the fraction of unaffected relatives of those with schizophrenia (bipolar disorder) who will not have the right (left) orbitofrontal type III and/or the right/left prominent/absent PCS.

3.5.15.1 Patients with schizophrenia and their unaffected relatives

A. The orbitofrontal type III in the right hemisphere:

	Schizophrenia present	Schizophrenia absent
Type III RH present	8	3
Type III RH absent	18	21

Positive predictive value = 8 / (8 + 3) * 100 = 72.7%
Negative predictive value = 21 / (18 + 21) * 100 = 53.9%
Sensitivity = 8 / (8 + 18) * 100 = 30.77%
Specificity = 21 / (3 + 21) * 100 = 87.5%

B. The left absent PCS variant:

	Schizophrenia present	Schizophrenia absent
Left PCS present	11	6
Left PCS absent	15	18

Positive predictive value = 11 / (11 + 6) * 100 = 64.7%
Negative predictive value = 18 / (15 + 18) * 100 = 54.54%
Sensitivity = 11 / (11 + 15) * 100 = 42.3%
Specificity = 18 / (6 + 18) = 75.0%

C. Present either type III in the right hemisphere or the left absent PCS variant or both of them:

It was also important to examine whether combination of both distinctive features – the right orbitofrontal type III and the left absent PCS variant – will influence positive and negative predictive values, as well as sensitivity and specificity. If this is the case then it might support the idea of combining structural features into the system of markers to increase prediction of schizophrenia in high risk individuals.

	Schizophrenia present	Schizophrenia absent
Type III or left PCS or both present	18	3
Type III or left PCS or both absent	8	21

Positive predictive value = 17 / (17 + 9) * 100 = 65.4%
Negative predictive value = 15 / (9 + 15) * 100 = 62.5%
Sensitivity = 17 / (17 + 9) * 100 = 65.4%
Specificity = 15 / (9 + 15) * 100 = 62.5%

3.5.15.2 Patients with bipolar disorder and their unaffected relatives

A. The orbitofrontal type III in the right hemisphere:

	Bipolar disorder present	Bipolar disorder absent
Type III RH present	7	2
Type III RH absent	19	19

Positive predictive value = 7 / (7 +2) * 100 = 77.8%

Negative predictive value = 19 / (19 + 19) * 100 = 50.0%

Sensitivity = 7 / (7 + 19) * 100 = 26.9%

Specificity = 19 / (2 + 19) * 100 = 90.5%

B. The orbitofrontal type III in the left hemisphere:

	Bipolar disorder present	Bipolar disorder absent
Type III LH present	9	4
Type III LH absent	17	17

Positive predictive value = 9 / (9 +4) * 100 = 69.2%

Negative predictive value = 17 / (17 + 17) * 100 = 50.0%

Sensitivity = 9 / (9 + 17) * 100 = 34.6%

Specificity = 17 / (4 + 17) * 100 = 80.95%

C. The left absent PCS variant:

	Bipolar disorder present	Bipolar disorder absent
Left PCS present	13	1
Left PCS absent	13	20

Positive predictive value = 13/(13 + 1) * 100 = 92.86%
Negative predictive value = 20/(13 + 20) * 100 = 60.6%
Sensitivity = 13/ (13 +13) * 100 = 50.0%
Specificity = 20 / (1 + 20) = 95.2%

D. The right absent PCS variant:

	Bipolar disorder present	Bipolar disorder absent
Right PCS present	16	10
Right PCS absent	10	11

Positive predictive value = 16/(16 + 10) * 100 = 61.5%
Negative predictive value = 11/(10 + 11) * 100 = 52.4%
Sensitivity = 16/ (16 +10) * 100 = 61.5%
Specificity = 11 / (10 + 11) = 52.4%

E. Present either type III in the right hemisphere or the left absent PCS variant or both of them:

It was considered to be important to examine whether combination of both distinctive features – the right orbitofrontal type III and the left absent PCS variant – will influence positive and negative predictive values, as well as

sensitivity and specificity. If this is the case then it might support the idea of combining structural features into the system of markers to increase prediction of bipolar disorder in high risk individuals.

	Bipolar disorder present	Bipolar disorder absent
Type III or left PCS or both present	18	3
Type III or left PCS or both absent	8	18

Positive predictive value = 18 / (18 + 3) * 100 = 85.7%
Negative predictive value = 18 / (8 + 18) * 100 = 69.2%
Sensitivity = 18 / (18 + 8) * 100 = 69.2%
Specificity = 18 / (3 + 18) * 100 = 85.7%

F. Present either type III in the left hemisphere or the right absent PCS variant or both of them:

	Bipolar disorder present	Bipolar disorder absent
Type III or right PCS or both present	23	13
Type III or right PCS or both absent	3	8

Positive predictive value = 23 / (23 + 13) * 100 = 63.9%
Negative predictive value = 8 / (3 + 8) * 100 = 72.7%
Sensitivity = 23 / (23 + 3) * 100 = 88.5%
Specificity = 8 / (13 + 8) * 100 = 38.1%

3.6 Conclusion

In this chapter the distribution of the orbitofrontal sulcogyral patterns and anterior cingulate morphology as well as the neuropsychological associations of the orbitofrontal patterns and the associations between the orbitofrontal patterns and paracingulate sulcus were examined in the Psychosis Study that included patients with schizophrenia and bipolar disorder and their unaffected relatives.

Orbitofrontal cortex

Analysis of the orbitofrontal sulcogyral patterns revealed an increased frequency of type III and a reduced frequency of type I in the right hemisphere in patients with schizophrenia and an increased frequency of type III in both right and left hemispheres with the reduction of type I in both hemispheres in patients with bipolar disorder compared to healthy controls. Importantly these findings were replicated in the Edinburgh High Risk Study (See **Chapter 4** for details) and in the Bipolar Family Study (See **Chapter 5** for details). Patients with schizophrenia and bipolar disorder differ from each other significantly in the distribution of type III in the left hemisphere. The distribution of the orbitofrontal sulcogyral patterns in unaffected relatives of patients with schizophrenia and bipolar disorder were similar to those in controls.

It is also vital to notice that a family history of mental illness might affect the distribution of the orbitofrontal patterns in the left hemisphere in patients with bipolar disorder and a family history of bipolar disorder only, in patients with bipolar disorder and a family history of both bipolar disorder and schizophrenia, and in patients with schizophrenia. It is notable that the orbitofrontal type III is not as frequent in the left hemisphere in the bipolar patients with a family history of both bipolar disorder and schizophrenia as in

other two groups. The distribution of the orbitofrontal type III in the left hemisphere of patients with bipolar disorder from mixed families could be placed in between the distribution of this pattern in patients with schizophrenia and its distribution in the bipolar patients with a family history of bipolar disorder only.

There was a gender effect found on the distribution of the orbitofrontal morphology suggesting that the distribution of the orbitofrontal patterns in the right hemisphere is more likely to be associated with males, while the distribution of the orbitofrontal patterns in the left hemisphere is more likely to be associated with females regardless of what diagnostic groups were compared.

Other important findings were related to symmetry of the orbitofrontal patterning (having the same orbitofrontal patterns in both right and left hemispheres). Healthy individuals appeared to have more symmetric orbitofrontal cortex than patients with schizophrenia (this result was replicated in the Edinburgh High Risk Study, see **Chapter 4** for details). Unlike patients with schizophrenia, patients with bipolar disorder were as symmetric as healthy controls with regards to the distribution of the orbitofrontal sulcogyral patterns.

Anterior Cingulate Morphology

Patients with schizophrenia or bipolar disorder did not vary from healthy individuals in distribution of the cingulate or paracingulate sulcus. However, patients with schizophrenia and bipolar disorder differed from their unaffected relatives in the distribution of the prominent paracingulate sulcus variant in the left hemisphere with an increased frequency of the left prominent paracingulate sulcus in unaffected relatives (38.5% in patients with schizophrenia and 66.7% in their unaffected relatives; 46.2% in patients with

bipolar disorder and 81.0% in their unaffected relatives). These findings were replicated in both high risk studies (for details in the Edinburgh High Risk Study see **Chapter 4**; for details in the Bipolar Family Study see **Chapter 5**). This suggests that the paracingulate sulcus could be a potential marker to distinguish those at high risk who will or will not develop an illness.

Further, there was a gender effect found on the prevalence of the prominent PCS as the female unaffected relatives of patients with schizophrenia had an increased frequency of the prominent paracingulate sulcus variant in the left hemisphere compared to its distribution in female patients themselves. On the contrary, female patients with bipolar disorder had an increased frequency of the PCS absent variant and a reduced frequency of the PCS prominent variant compared to their female unaffected relatives. Similar differences were correct for male individuals in the right hemisphere.

There was a gender effect found on the distribution of the cingulate sulcus. Female healthy individuals had an increased frequency of the connected CS (presented as one piece) while female unaffected relatives of patients with schizophrenia were more likely to have an increased frequency of the disconnected CS (presented in many pieces) in the right hemisphere. A further issue was the fact that the cingulate sulcus did not share a gender effect with the paracingulate and orbital sulci. The distribution of the cingulate pieces in the right hemisphere were more likely to be associated with female participants while the distribution of the orbitofrontal patterns and the paracingulate sulcus in the right hemisphere were more likely to be associated with males individuals.

Furthermore, healthy individuals tended to be more symmetric in both CS and PCS morphology compared to all patient groups and their unaffected relatives with the biggest difference between healthy controls and patients

with schizophrenia. Importantly, the patient groups were less symmetric when compared to their unaffected relatives.

Apart from the symmetry – asymmetry issue there is a subject of continuity of orbital or cingulate sulci when healthy individuals were more likely to have a single continuous cingulate sulcus in both hemispheres, while patients with schizophrenia and unaffected relatives of patients with bipolar disorder tend to have a 'disconnected' ('broken') cingulate sulcus with 2 or 3 pieces (segments). The unaffected relatives of patients with schizophrenia were more likely to have the cingulate sulcus as one piece while patients with schizophrenia had mostly disconnected CS in the right hemisphere.

Associations between OFC and ACC

There is an indication in this data of an association between the orbitofrontal and anterior cingulate morphology in the right and left hemispheres. For example, healthy individuals with type II in the left hemisphere were more likely to be in a possession of the connected cingulate sulcus in the right hemisphere compared to those participants that were without the orbitofrontal type II in the left hemisphere. Unaffected relatives of the schizophrenia patients with the orbitofrontal type I or/and without type III in the right hemisphere were less likely to have the paracingulate sulcus being absent in the right hemisphere compared to those unaffected relatives of patients with schizophrenia that were without the orbitofrontal type I or with the orbitofrontal type III in the right hemisphere. Patients with bipolar disorder had the orbitofrontal sulcogyral patterns being associated with the cingulate cortex in the same hemisphere as well as in the opposite one. The bipolar patients with the orbitofrontal type III in the right hemisphere were more likely to have the prominent paracingulate sulcus in the right hemisphere compared to those patients with bipolar disorder that were without the orbitofrontal type III in the right hemisphere. There was also an association found between the

orbitofrontal type III in the left hemisphere and the right prominent PCS in such a way that those bipolar patients with the orbitofrontal type III in the left hemisphere were more likely to have the prominent paracingulate sulcus in the right hemisphere compared to those patients with bipolar disorder that were without the orbitofrontal type III in the left hemisphere.

There was an interesting observation made related to the connectivity of the orbitofrontal morphology and the connectivity of the anterior cingulate morphology. For example, healthy individuals with the orbitofrontal type I (half-connected, half-disconnected pattern) in the left hemisphere were more likely to be in a possession of the connected cingulate sulcus in the left hemisphere while those healthy individuals with the orbitofrontal type III (mostly disconnected pattern) in the left hemisphere were more likely to be in a possession of the disconnected cingulate sulcus in the left hemisphere. Even the schizophrenia patients with the orbitofrontal type I in the left hemisphere were more likely to be in possession of the connected cingulate sulcus in the right hemisphere compared to those patients with schizophrenia that were without the orbitofrontal type I in the left hemisphere. The bipolar patients with the orbitofrontal type I and/or without the orbitofrontal type II in the right hemisphere were more likely to have the connected cingulate sulcus in the right hemisphere compared to those patients with bipolar disorder that were without the orbitofrontal type I or with the orbitofrontal type II in the right hemisphere. Further, unaffected relatives of bipolar patients with the orbitofrontal type I and/or without the orbitofrontal type III in the right hemisphere were more likely to have the connected cingulate sulcus in the left hemisphere compared to those unaffected relatives of patients with bipolar disorder that were without the orbitofrontal type I or with the orbitofrontal type III in the right hemisphere. The similarity of these associations between the orbitofrontal and cingulate morphology in various diagnostic groups suggests that the nature of such associations may not be

diagnosis related but be a characteristic of the orbitofrontal sulcogyral patterns and cingulate sulcus variants themselves.

Associations between cingulate and paracingulate sulcus were found either in the same hemisphere (between the left cingulate sulcus and the left present paracingulate sulcus in patients with schizophrenia), or between the opposite hemispheres (the left cingulate sulcus and the right paracingulate sulcus in patients with bipolar disorder or the right cingulate sulcus and the left paracingulate sulcus in unaffected relatives of patients with bipolar disorder).

Neuropsychological associations

The results of the neuropsychological associations of the orbitofrontal morphology suggests that despite the wider distribution of the orbitofrontal type I in the healthy population (was discovered in 56% of healthy hemispheres, according to Chiavaras and Petrides, 2000) this pattern is not cognitively the 'brightest' between the orbitofrontal patterns. The more connected type II (was discovered in 30% of healthy hemispheres) scored higher in the WASI IQ in healthy individuals. For example, the WASI verbal IQ scores were: mean = 108.29 (SD = 13.077) in those with type I, mean = 118.30 (SD = 8.015) in those with type II, and mean = 105.80 (SD = 17.598) in those with type III in the right hemisphere. Moreover, the schizophrenia patients with the orbitofrontal type II seemed to have better chances to have their cognitive functions preserved compared to patients with the other orbitofrontal patterns. In the schizophrenia patients from the study of seven groups the verbal IQ scores were: mean = 98.36 (SD = 12.971) in those with type I, mean = 107.33 (SD = 9.913) in those with type II, and mean = 95.38 (SD = 8.228) in those with type III in the right hemisphere. However, patients with bipolar disorder with the orbitofrontal type III in either hemisphere seemed to preserve their cognitive abilities better than the bipolar patients

with any other orbitofrontal pattern (the WASI verbal IQ scores were: mean = 108.67 (SD = 13.048) in those with type I, mean = 103.75 (SD = 17.951) in those with type II, and mean = 112.14 (SD = 11.082 in those with type III in the right hemisphere; and mean = 107.14 (SD = 15.060) in those with type I, mean = 105.86 (SD = 12.522) in those with type II, and mean = 110.56 (SD = 12.228 in those with type III in the left hemisphere).

Although, healthy individuals with the orbitofrontal type III in either hemisphere had lower IQ than those without type III, the problem did not appear to be with memory. Healthy controls and, especially, patients with schizophrenia with the orbitofrontal type III in either hemisphere performed better on the Rivermead Memory test compared to the other patterns (for example, total profile score was: mean = 24.85 (SD = 3.363) for type I, mean = 25.57 (SD = 4.353) for type II, and mean = 32.40 (SD = 6.465) for type III in the left hemisphere in patients with schizophrenia). In patients with bipolar disorder those with the orbitofrontal type II (and not with type III) performed better on the Rivermead Memory test (total profile score was: mean = 26.00 (SD = 8.113) for type I, mean = 32.00 (SD = 6.976) for type II, and mean = 25.57 (SD = 2.820) for type III in the right hemisphere).

Further, executive functions associated with different orbitofrontal patterns were also examined using the Hayling Sentence Completion Task. In healthy controls and patients with schizophrenia those with the orbitofrontal type II in the right hemisphere performed worse in the Hayling Sentence Completion Task compared to those with the other types making more errors and requiring more time to complete the test. However, in patients with bipolar disorder, those with the orbitofrontal type II in the left hemisphere performed worse in the Hayling Sentence Completion Task compared to those with the other types making more errors and requiring more time to complete the test.

Also there was not any significant associations found those with the orbitofrontal type III in either hemisphere scored higher in the Young Mania Rating Scale overall compared to participants with any other type (mean = 2.20 (SD = 3.816) for the orbitofrontal type I, mean = 1.64 (SD = 3.163) for type II, and mean = 3.30 (SD = 6.292) for type III in the right hemisphere). Furthermore, the bipolar disorder patients with the orbitofrontal type III in the left hemisphere scores higher in the Hamilton Depression Rating Scale.

The calculated positive predictive value for the orbitofrontal type III in the right hemisphere was 72.7% for schizophrenia and 77.8% for bipolar disorder. The calculated positive predictive value for the paracingulate sulcus in the left hemisphere was 92.86% for bipolar disorder. These results suggest importance of the orbitofrontal sulcogyral patterns and the paracingulate sulcus for predictability of schizophrenia and bipolar disorder.

Application of the BrainVISA software automated sulci recognition pipeline was the beginning of a search for the ways to make the orbitofrontal sulcogyral pattern identification more accessible.

The results described in this chapter will be further discussed in chapter 8 of this thesis.

Limitations of the study presented in this chapter

There are a number of difficulties to be concern either when applying manual sulci identification protocol or when involving automatic sulci recognition software. Firstly, a variability of sulcogyral morphology across individuals, which is particularly well - known in the orbitofrontal area, might affect the results of manual sulci identification. Further, the highly variable junctions between sulci as well as the spatial relationship between sulci and gyri of the cerebral cortex might also increase the complexity of the identification

process for the automatic sulci recognition pipeline. This makes the extension of the sulcal pattern classification to new cortical regions problematic.

Chapter 4

Distribution and functional associations of orbitofrontal sulcogyral patterns in subjects at high genetic risk of developing schizophrenia as well as associations between orbitofrontal patterns and anterior cingulate morphology

This chapter describes orbitofrontal morphology and its association with the paracingulate sulcus, brain volume and neuropsychological scores in the Edinburgh High Risk Study as well as the symmetry - asymmetry scores and the gender effect on the orbitofrontal morphology. Included positive and negative predictive values and sensitivity tests suggest that sulcogyral morphological variants in combination with the anterior cingulate morphology predict the development of mental illness.

Chapter 4 OFC in the EHRS

4.1 Introduction

Alterations of orbitofrontal sulcogyral patterns have been previously reported in schizophrenia (Nakamura *et al.,* 2007), as well as anterior cingulate morphology has been found to be associated with this debilitating illness (Crosson *et al.,* 1999; Fornito *et al.,* 2006; Huster *et al.,* 2009). Both orbitofrontal and paracingulate sulci are formed at about the same period of gestation while cingulate sulcus is developing earlier around 20th ontogenic week (Chi *et al.,* 1977; Armstrong *et al.,* 1995). Being known as tertiary orbitofrontal and paracingulate sulci might be more influenced by the environmental factors than genetic abnormalities. Keeping in mind that their formation takes place at the same period of time both orbitofrontal and paracingulate sulci could be affected by similar factors and might demonstrate comparable neuro-psychological associations. Being developed during such early period these sulci do not change their shape later. Given this, the combination of the orbitofrontal patterns and the paracingulate sulcus could be applied for prediction of psychosis.

The existence of 'markers' was suggested by the neurodevelopmental model of schizophrenia. According to this model the markers could identify individuals who will subsequently become ill. Structural variations of the orbitofrontal and paracingulate morphology might represent a possible objective anatomical measure that could reflect aberrant neurodevelopment and be used to detect schizophrenia pre-morbidly. However, there were no publications so far on whether both orbitofrontal and paracingulate sulci could represent a part of the markers system in order to improve prediction of the mental illnesses. This is why in this chapter it was attempted to establish whether the orbitofrontal sulcogyral patterns in combination with paracingulate variants might predict psychosis. In order to achieve this, the distribution of orbitofrontal patterns, their

neuropsychological and clinical associations, and the associations between orbitofrontal patterns and anterior cingulate morphology was examined in those at high genetic risk of developing schizophrenia.

4.1.1 The orbitofrontal cortex

The human orbitofrontal cortex is a multifunctional region which is known to play an important role in emotional processing, including hedonic experience and memory (Ongur and Price, 2000; Kringelbach, 2005). This region may also be involved in the affective evaluation of reinforcers, decision - making, motivation and goal - directed behaviour (Holland and Gallagher, 2004; Walton *et al.,* 2004). Human brain lesion studies have associated orbitofrontal cortex lesions with social withdrawal, apathy, socially inappropriate behaviour, impairment in the identification of emotional face expression, affective instability and depressed mood (Grafman *et al.,* 1986; Grafman *et al.,* 1996; Rolls, 1996). Pang and Lewis (1996) found clear similarities between symptoms associated with schizophrenia and those arising from lesions of the orbitofrontal cortex. Moreover, a number of studies have demonstrated the alteration of cognitive functions such as emotional processing and memory in schizophrenia (Schneider *et al.,* 1995; Stip, 1996).

The orbitofrontal cortex is widely interconnected with other brain regions including the amygdala, cingulate and striatum. As these areas are believed to be important in the development of schizophrenia it is possible to suggest that the alteration of orbitofrontal morphology may contribute to the symptomatology of schizophrenia (Amaral and Price, 1984; Mesulam and Mufson, 1984; Morecraft *et al.,* 1992; Van Hoesen *et al.,* 1993; Carmichael and Price, 1995 a; Eblen and Graybiel, 1995; Rolls, 1999 b). Some evidence from structural MRI

studies report volume changes in the prefrontal cortex (Lacerda *et al., 2*007) and abnormalities of the orbitofrontal surface (Nakamura *et al.,* 2007) in individuals with schizophrenia. A number of longitudinal studies of people at high genetic risk of developing mental illnesses discovered that those participants who developed psychosis had reduced grey matter volume in several regions including the orbitofrontal cortex (Pantelis *et al.,* 2003; Borgwardt *et al.,* 2008).

4.1.2 The anterior cingulate cortex

The anterior cingulate cortex (ACC) is located in the middle frontal lobe, includes Brodmann' areas 24, 25 and 33 and is known to be involved in affective regulation (the rostral part) and cognitive modulation (the caudal part) (Bush *et al.,* 2000; Yucel *et al.,* 2003). Moreover, the ACC was found associated with such cognitive functions as the initiating aspect of attention (Fernandez-Duque and Posner, 2001), inhibition of prepotent responses (Barch *et al.,* 2002) and working memory (Cabeza and Nyberg, 2000). Considering that genetic and neurodevelopmental influences may lead to the morphological abnormalities of the brain as well as cognitive deficits (Curry *et al.,* 1997), it might be possible to connect variability of the anterior cingulate morphology and cognitive functioning. Supporting this, Frangou and colleagues (2004) found a positive correlation between general intellectual ability and grey matter density in different brain regions including the cingulate gyrus.

The anterior cingulate region is known to be connected to such brain areas as the thalamus, hippocampus and amygdala (Likhtik *et al.,* 2005; Vogt, 2005). Intriguingly, there could be interconnection between the anterior cingulate region and the lateral orbitofrontal cortex through the thalamus (Klein *et al.,* 2010). Such connections could explain functional relationship of these two areas: while

the OFC is involved with the representation of reward outcomes and with associating of the stimulus and object with reward, the ACC is engaged in reward - guided planning of actions, the generation of new strategies and the detection of reward prediction errors (Klein *et al.,* 2010). Moreover, a number of studies reported differences in the anterior cingulate morphology in patients with schizophrenia involving only male participants. Rametti and colleagues (2010) found a gender effect on structural abnormalities in the anterior cingulate region. Considering that the orbitofrontal and paracingulate cortex develop at the same time during the 3rd trimester of pregnancy (Chi *et al.,* 1977; Kostovic and Jovanov - Milosevic, 2006) and that these two regions might be connected with each other (Carmichael and Price, 1995 a, b; Klein *et al.,* 2010), it is possible to suggest that the gender effect that was reported for the ACC could be applied to the OFC as well.

Research from several fields suggests an important role of the orbitofrontal and cingulate cortex in the pathophysiology of schizophrenia. However, the orbitofrontal region has been relatively ignored in schizophrenia research. Furthermore, no attention has been paid to any association between structural abnormalities in orbitofrontal and anterior cingulate regions. Given this gap in the research field, further investigation of orbitofrontal morphology, its neuro - psychological associations and its relations with the paracingulate sulcus in schizophrenia might have the potential to deliver important insights into this mental illness.

4.1.3 Schizophrenia

This disorder and the findings associated with it, especially those related to the orbitofrontal and cingulate regions, were described in greater detail in **Chapter 2** of this thesis.

4.1.4 Neuropsychological dysfunction of relatives with schizophrenia

Neuropsychological deficits have been previously reported in relatives of patients with schizophrenia (Byrne *et al.,* 1999). The affected functions included verbal fluency, memory, executive function and sustained attention. For more details see **Chapter 2** of this thesis.

4.1.5 The Edinburgh High Risk Study

The Edinburgh High Risk Study (EHRS) provided with an opportunity to investigate the orbitofrontal and cingulate morphology. The EHRS is a longitudinal study of individuals at genetically high risk of developing schizophrenia. They were initially scanned when well, and then followed up during the period of about 10 years so they could be observed in time when those at high risk would be most likely to develop schizophrenia. Age - matched healthy volunteers and subjects in their first episode of schizophrenia were also included to compare the distribution of the orbitofrontal patterns (Chakirova *et al.,* 2010) and the anterior cingulate morphology (Meredith *et al.,* 2012) between the groups. So, overall one hundred and forty - six participants at high genetic risk of developing schizophrenia, thirty four patients in their first episode of schizophrenia, and thirty six healthy controls were recruited, scanned and clinically assessed. The orbitofrontal sulcogyral patterns in each hemisphere of

these subjects were categorized according to the classification system suggested by Chiavaras and Petrides (2000). The Yucel's method was applied to rate the anterior cingulate morphology in either hemisphere of the participants in the Edinburgh High risk Study. The distribution of the orbitofrontal patterns and the cingulate and paracingulate variants were compared between the mentioned three groups, as well as between those high - risk subjects who did and did not develop schizophrenia. The relationship between the OFC patterns and the anterior cingulate morphology, the influence of gender on both areas of the brain, structural and neuropsychological associations of the orbitofrontal morphology, and positive and negative predictive value of the markers as well as sensitivity of the test were explored.

4.2 Methods

4.2.1 Participants

The Edinburgh High Risk Study is a longitudinal study of individuals at high genetic risk of developing schizophrenia. It started by recruiting young people with one first - or two second - degree relatives affected by schizophrenia. Two groups were formed: high - risk subjects and controls aged between 16 and 25 years. This means that in the following 10 years they passed through the age of greatest risk of developing schizophrenia. The recruitment and follow - up process have been described previously in detail elsewhere (Hodges *et al.,* 1999; Johnstone *et al.,* 2000; Johnstone *et al.,* 2005). In brief, all participants went through a detailed neuropsychological and clinical assessment, and a structural Magnetic Resonance Imaging (sMRI) of the brain at the beginning of the study. The assessment included the Structured Inventory for Schizotypy (SIS) and Rust Inventory of Schizotypal Cognitions (RISC) as well as Stroop Colour Word Test (Golden, 1978) and Rey Auditory Verbal Learning Test (Rey, 1964). Their premorbid intelligence level was measured using the National Adult Reading Test (NART). Especial attention in the present study was paid to the SIS and RISC scores as those measures have previously been found to be predictive of schizophrenia in the Edinburgh High Risk Study (Johnstone *et al.,* 2005). The neuropsychological assessment and its main findings in the EHRS were previously described elsewhere (Cosway *et al.,* 2000; Johnstone *et al.,* 2002; Whyte *et al.,* 2006). High risk participants were well when they were scanned and assessed, and none of them had received antipsychotic treatment. Control subjects did not have any personal or family history of mental illnesses, or trauma and brain growth abnormalities, and were not on antipsychotic

medication. Patients in their first episode of schizophrenia were receiving antipsychotic drugs.

The most important feature of the EHRS is that the high risk individuals were scanned while they were well and then were followed up prospectively for a period of 10 years using repeated structured clinical assessments such as the Present State Examination (PSE). At time of entry into the study none of the subjects were seeking help and therefore this study contains premorbid information on people who later develop schizophrenia. All of those participants who later developed schizophrenia fulfilled the diagnostic criteria of the International Classification of Diseases 10th Revision (ICD – 10; WHO, 1992). In a summary of the data, 146 high risk participants provided baseline data including MRI scan, 143 subjects had a completed RISC, and 138 high risk subjects had a SIS. Thirty six control individuals were recruited from the social networks of the high risk participants. Additionally, there were 34 patients in their first episode of schizophrenia recruited from admissions to psychiatric hospitals in Lothian Region, Scotland, and involved as a comparison into the EHRS.

In the duration of the EHRS seventeen of the high risk subjects who had been successfully scanned developed schizophrenia, fulfilling ICD-10 criteria (Johnstone *et al.,* 2005). All demographic details of the participants are in **Figure 4.2.**

4.2.2 MRI scanning

The participants went through the MRI brain scanning on a 1.0 Tesla Magnetom (Siemens, Erlangen, Germany) scanner. In order to minimize head movements the foam padding and velcro straps across the forehead and chin were applied.

Midline sagittal localization, orientating to the anterior commissure – posterior commissure (AC-PC) line, was followed by two sequences to image the whole brain. The first scan was a double spin - echo sequence that gave simultaneous proton density and T2-weighted images (repetition time [TR] = 3565 msec, echo time [TE] 20 and 90 msec, 31 contiguous 5 mm slices acquired in the Talairach plane, field of view 250 mm), which were used to exclude any gross brain lesions. The second scan (for the volumetric analysis of whole brain and regions) was a fast gradient - echo sequence consisting of a 180^{o} inversion pulse followed by a Fast Low Angle Shot collection (flip angle: 128, TR = 10 msec, TE = 4 msec, time to inversion [TI] = 200 msec, relaxation delay time = 500 msec, field of view = 250 mm) giving 128 contiguous 1.88 - mm thick slices in the coronal plane orthogonal to the Talairach plane. Any inhomogeneity in the head coil was corrected for after scanning a flood phantom (see Whalley *et al.,* 1999 for further details). To ensure the reliability of the scan sequences over the course of the study regular phantom scanning was employed.

Established image pre-processing operations used in the assessment of OFC patterns are described in detail by Moorhead and colleagues (2006). In order to perform pre-processing functions on images in this study the Statistical Parametric Mapping (SPM) package (http://www.fil.ion.ucl.ac.uk/spm) was used. Firstly, the T1 candidate scans were segmented in native space using the SPM segment function. Secondly, after the segmentation the SPM brain extraction function recovered a tissue mask for each scan. In order to give each brain a T1 tissue image with removed nonbrain tissue and cerebrospinal fluid, those tissue masks were combined with the native T1s. In order to obtain the AC - PC registration while maintaining the native space volumes the SPM coregistration function was used to provide a 9 - point affine mapping of the extracted brains into the Montreal Neurological Institute (MNI) space. Then this mapping into the

MNI space was applied to the brain tissue mask, the original T1s, and the three native space segments without size or shape adjustment. After that these AC - PC registered images were resliced to 1 x 1 x 1 mm voxel size and were used to classify the orbitofrontal sulcogyral patterns and anterior cingulate morphology.

4.2.3 Neuropsychological and clinical assessment

4.2.3.1 The positive and Negative Symptoms Scale

One of the assessments undertaken by participants in this study was the positive and negative symptom scale (PANSS, Kay *et al.,* 1987). This is a 30 item scale derived partly from the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham, 1962). The scale is subdivided into three subcategories, including positive, negative and general psychopathology (See **Figure 4.1**). A glossary definition is used to rate each item.

Figure 4.1. The individual items of each scale of the positive and negative symptoms scale. Rating of individual items: 1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = extreme.

Subscales:	**Positive**	**Negative**	**General Psychopathology**
Individual items:	Delusions	Blunted affect	Anxiety
	Conceptual disorganization	Poor rapport	Tension
	Hostility	Emotional withdrawal	Poor attention
	Excitement	Difficulty in abstract thinking	Depression
	Hallucinatory behaviour	Passive/ apathetic social withdrawal	Somatic concern
	Grandiosity	Stereotyped thinking	Guilt feeling
	Suspiciousness/persecution	Lack of spontaneity and flow of conversation	Mannerism and posturing
			Motor retardation
			Uncooperativeness
			Disorientation
			Preoccupation
			Active social avoidance
			Poor impulse control
			Lack of judgement and insight
			Unusual thought content
			Disturbance of volition

4.2.3.2 The National Adult Reading Test

See the description of the test in **Chapter 3** of this thesis.

4.2.3.3 The Stroop Colour Word Test

One of the tests used to assess the participants in this study was the Stroop Colour Word Test. The applied in the EHRS version of the Stroop test was the one developed by Golden (1978). This test is known for its sensitivity to frontal lobe disorders and its short administration time. The Stroop Colour Word Test was described in greater detail in Spreen and Strauss (1991). In brief, this well - known cognitive test measures the ease with which participants can shift perceptual set to adjust it to changing demands and suppress a habitual response in a favour of an unusual one. A response was recognised as habitual when it indicated the colour of the letters. A response was acknowledged as unusual when it indicated the colour of the letters despite the fact that those letters spell a different colour – word. This measure of cognitive flexibility was based on the effect that was originally described by John Ridley Stroop in the article 'Studies of interference in serial verbal reactions' in 1935.

The Stroop test consisted of three cards with 10 rows of five items in each of them. The test was subdivided into four parts. In the first part the subject was presented and asked to read randomized colour names such as blue, red, green and yellow that were printed in black type. In the second part the subject was presented with the same colour names but printed in colour ink (red, yellow, blue and green) and was asked to read them ignoring the colour of the print. In this part the colour of the print never corresponded to the name of the colour. In the third part the subject was presented with the coloured dots (yellow, green, red

and blue) and asked to name the colour of the dots. In the fourth part the subject was presented with the same cards as in the second part and asked to name the colour of the print ignoring the colour names.

The test demonstrates interference in the reaction time meaning a delay in the processing of the word's colour and therefore a slower reaction times and increased number of errors, when such a word as blue, green or red is printed in a colour different from the colour expressed by the semantic meaning of the word (difference in the reaction time between parts 2 and 4; this effect is although named 'colour-word interference effect').

The Stroop test was previously applied to examine patients with schizophrenia, Huntington's disease and Parkinson's disease (Batchelor *et al.,* 1995; Hanes *et al.,* 1996) as the Stroop interference effect was found greater in patients with frontal lobe dysfunction (Perrett, 1974; Stuss *et al.,* 2001 b).

4.2.3.4 The Rey Auditory - Verbal Learning Test

The Rey Auditory - Verbal Learning Test (RAVLT) was designed to assess verbal learning and memory. This is a brief pencil-and-paper measure that examines immediate memory span, recognition memory, susceptibility to interference and new learning. The original version of this test was developed by Andre Rey in 1964. This version was further altered and adapted for use with English-speaking people by Taylor (1959) and Lezak (1995). The latest was applied to the participants in the EHRS and consisted of 15 nouns (List A) that the tester read aloud for five consecutive trials with fixed order of the words in each of the trials. The subject was asked to recall those nouns after every trial. After the fifth trial the tester presented to the participant interference list of 15

words (List B) and asked the subject to repeat it. Immediately after that as well as after a 20 - minutes delay period the subject is asked to recall List A. Finally, the story was presented where all the nouns from the List A were used and the subject was required to recognize words from the list.

The results of this test could be used to differentiate various memory disorders. Those with a generalized memory deficit are known to perform poorly on the recognition trial and free recall (Rey, 1964; Lezak, 1983; Bleecker *et al.,* 1988).

4.2.3.5 The Rust Inventory of Schizotypal Cognitions

The Rust Inventory of Schizotypal Cognitions (RISC) is a short objective inventory designed to assess the cognitive content that might be associated with schizophrenia and schizotypal personality disorder. The inventory contains of twenty six statements to which the participant was required to respond. These statements were designed to identify bizarre and eccentric thought patterns. The RISC is an important instrument for clinical assessments and for academically psychiatric research.

4.2.3.6 The Structured Inventory for Schizotypy

The Structured Interview for Schizotypy (SIS) was developed by Kendler (Kendler, *et al.,* 1989). This interview was found to be able distinguishing between the relatives of healthy individuals and relatives of patients with schizophrenia. The SIS was subdivided into two main sections, representing ‘symptoms’ and ‘signs’. The section ‘symptoms’ was a semi-structured interview, while the section ‘signs’ was rated after the interview and reflected the observed behaviour of the participant. The section ‘symptoms’ included such items as

social anxiety, social isolation/introversion, ideas of reference, sensitivity, restricted emotion, illusions, magical thinking, suspiciousness, psychotic-like symptoms, adult antisocial traits, derealisation and depersonalization, irritability and impulsivity. The section 'signs' consisted of the items including affect, organization of speech and thought, rapport, suspiciousness and odd, eccentric behaviour. Each question was assigned by individual score. A total score was generated by adding the scores from each item. A global score of between 1 (marked) and 7 (absent) was allocated for each section that was listed above. The SIS was divided by factor analysis into four component factors: psychotic symptoms, social withdrawal, odd behaviour, and socio-emotional dysfunction, as previously described in (Miller *et al.,* 2002).

4.2.4 Classification of orbitofrontal sulcogyral patterns

The protocol of sulcogyral patterns classification based on that proposed by Chiavaras and Petrides (2000) was developed and was later further enhanced by Chakirova and colleagues (2010). In greater details the protocol could be found in the **Appendix III** and **Chapters 1** and **3** of this thesis. See also **Figure 1.4** in the **Chapter 1** of this thesis.

4.2.5 Identification of the cingulate and paracingulate sulci morphological variances

To perform the CS and PCS classification protocol, firstly, the medial brain surface sulci were identified using the "MRIcro" software package freely available on http://www.sph.sc.edu/comd/rorden/mricro.html, then confirmed and measured using "Analyze" software (Mayo Foundation, Rochester, MN).

There are two previously developed protocols for ACC classification: Paus' and Yucel's protocols (Paus *et al.,* 1996; Yucel *et al.,* 2001). The difference between those two protocols is in the variety of the sulcal forms included into the classification categories (Leonard *et al.,* 2009). In order to classify the CS and PCS in the EHRS the criteria described by Yucel and colleagues (2001) were applied as this protocol is known as more reliable (Leonard *et al.,* 2009). The protocol was obtained from the authors; also described in references (Slagle *et al.,* 1989; Rahm *et al.,* 2006; Broome *et al.,* 2009). In order to identify the paracingulate and cingulate sulci from 3 to 4 consecutive sagittal slices were examined starting from the interhemispheric fissure and moving laterally into the brain tissue. According to the protocol sulcal segments had to be evident and distinguishable from the superficial cortical dimples. The correct identification of each sulcus had to be confirmed using the axial and coronal sections of the brain. These were also supposed to help to exclude superficial cortical dimples from the analyses.

The cingulate sulcus was considered to be interrupted into segments if there was present a clear gap on several sagittal sections (Leonard *et al.,* 2009). Importantly, this gap had to be confirmed using coronal section; otherwise the cingulate sulcus was identified as a single or continuous sulcus. The number of segments of the cingulate sulcus was recorded counting from the sulcus origin anterior to the genuine of the corpus callosum to its posterior marginal ramus branch.

The paracingulate sulcus was identified using the sagittal slices as this sulcus starts immediately dorsal and runs parallel to the cingulate sulcus. Following the previously developed protocol (Yucel *et al.,* 2001) the PCS morphological

variants were subdivided into three groups according to their anterior-posterior extent and their presence:

1. The PCS variant was named ‘prominent’ if it was more than 40 mm in length;
2. The PCS variant was called ‘present’ when the sulcus piece(s) were more than 20 mm in length;
3. The PCS variant was considered ‘absent’ if PCS was not identifiable at all or it was less than 20 mm in length.

There were some other details in the protocol regarding to the rating of the PCS morphological variants. For example, only the PCS segments that were more than 10 mm in length were included. In order for the PCS variant to be classified as ‘present’ at least one segment supposed to be about 20mm in length. Where a single segment was more than 40 mm in length the PCS was rated as ‘prominent’. However, when the total length of the PCS was more than 40 mm but the total gaps between segments were measured more than 20 mm this variant was rated as ‘present’.

4.2.6 Reliability of the anterior cingulate morphology identification protocol

Two raters used the protocol until confident and then rated the same 25 randomly chosen scans (50 hemispheres). Left/right inter - rater reliability was 1.00/0.933 for CS classification and 0.80/0.80 for PCS classification respectively. Then, one rater proceeded with the classification of the cingulate sulcus, while the other rater identified the paracingulate sulcus on the 216 images (432 hemispheres) in this study. Left/right intra - rater reliability was

assessed in a subset of 15 scans (30 hemispheres) and were 1.00/1.00 for the cingulate and 0.91/0.87 for the paracingulate sulcus classification.

4.2.7 Reliability of the OFC patterns classification protocol

The classification of the orbitofrontal sulcogyral patterns was carried out by G.C., blinded to subject group. Inter-rater reliability was assessed by two raters (G.C., K.W.), who independently evaluated the sulcal patterns for 15 random cases (30 hemispheres: 15 in the right and 15 in the left), blinded to group membership. The intra-class correlation coefficients were 0.86 for right hemisphere and 0.84 for left hemisphere. Moreover, despite this acceptable reliability, all scans were reviewed by G.C. and K.W. together, with any disagreements about the orbitofrontal pattern ratings being resolved by discussion until consensus was reached.

4.2.8 Statistical analysis

All statistical analyses were performed using the Statistical Program for the Social Sciences (SPSS, Chicago, Illinois) version 19 (http://www.spss.com/software).

Analysis of variance and chi-squared tests were applied to compare demographics between the groups. The distribution of the orbitofrontal sulcogyral patterns in the various groups were analysed using Pearson chi-squared analysis. The distribution of the orbitofrontal morphology was compared firstly with both hemispheres combined. Secondly, the data was examined in each hemisphere separately (Chakirova *et al.,* 2010). Justification for such type of analyses especially for combining hemispheres was given by Nakamura and

colleagues (2007). Initially, the number of participants with particular orbitofrontal type (I, II and III) in each hemisphere were compared separately and in both hemispheres combined between the all three groups: patients in their first episode of schizophrenia, the high risk participants and healthy controls. In order to examine the origin of the difference pairwise comparison of the orbitofrontal patterns was conducted between patients in their first episode of schizophrenia and all other participants (healthy controls and the high risk participants combined). Considering that orbitofrontal types I and III were previously found to be altered in patients with schizophrenia (Nakamura *et al.,* 2007) the number of the orbitofrontal type I and type III in the two hemispheres combined were also analysed and compared between groups of participants of particular interest. In order to facilitate comparison with previously published findings (Chiavaras and Petrides, 2000; Nakamura *et al.,* 2007), separate comparisons within right and left hemispheres were included. The contrasts of interests were: healthy controls versus patients in their first episode of schizophrenia, and high risk individuals who developed schizophrenia versus those at high risk who did not.

The gender effect on the distribution of the orbitofrontal and anterior cingulate morphology, the symmetry – asymmetry comparison of the orbitofrontal and anterior cingulate morphology between the groups, the distribution of the cingulate and paracingulate sulcul morphological variants between the groups and associations between orbitofrontal and anterior cingulate morphology were analysed using Kruskal-Wallis test.

Through **Chapters 3**, **4** and **5** of this thesis neuropsychological and structural association analyses of the orbitofrontal morphology were examined in a number of different cohorts. The purpose of it was to investigate whether there

are some replicable features of the orbitofrontal patterns. These analyses included the examination of the relationships between the possession of particular orbitofrontal type and scores on the SIS (both total and factor scores), the RISC scores, the results of the Stroop Colour Word Test and the Rey Auditory Verbal Learning Test within the group of those at high genetic risk of developing schizophrenia. In undertaking these analyses priority was given to the examination of hemispheres separately with an exception of some clinical measures when hemispheres were combined as well (the RISC and the SIS). To enable the examination of any associations with combined hemispheres, participants were divided into those expressing type III in either hemisphere and those without this orbitofrontal pattern. In these two groups ratings on the RISC and the SIS scores were compared using the independent *t*-test, adjusted for multiple comparisons. The performance of participants at high genetic risk of developing schizophrenia possessing different orbitofrontal sulcogyral patterns were examined using the Stroop Colour Word Test and the Rey Auditory Verbal Learning Test. To consider the gender effect on the orbitofrontal morphology and its associations the gender*orbitofrontal pattern interactions in the high risk group were analysed. The associations of the orbitofrontal sulcogyral patterns with the previously extracted volumes of different brain regions (Lawrie *et al.,* 2001) and fronto - parietal connectivity (Whalley *et al.,* 2005 b) were also examined calculating the orbitofrontal patterns by gender interactions with the volumes of different brain regions and fronto - parietal connectivity as dependent variables. Evaluations of the positive and negative predictive values as well as sensitivity and specificity are provided in the section **4.3.11** of this **Chapter**.

4.3 Results

4.3.1 Demographics

The main groups did not differ significantly for age, gender, handedness or IQ (See **Figure 4.2**).

Figure 4.2. Demographics of the main comparison groups. CON = well controls; HR = high-risk; SCZ = first-episode schizophrenia. Demographic variables are similar in all the main comparison groups (all $p > 0.05$).

Demographics of the main comparison groups				
	CON (n = 36)	**HR** (n = 146)	**SCZ** (n = 34)	**P value**
Age (mean + / - SD)	21.2 + / - 2.4	21.2 + / - 2.92	21.6 + / - 3.63	0.7
Gender (male : female)	17 : 19	74 : 72	22 : 12	0.3
Handedness (right : left : mixed)	31 : 3 : 2	129 : 9 : 6*	31 : 1 : 2	0.8
NART (mean + / - SD)	105.47 + / - 14.13	98.39 + / -12.85	88.17 + / - 14.76	0.92

*handedness data missing for 2 individuals.

4.3.2 The distribution of the OFC patterns between the main groups

Type IV was present in either hemisphere in three healthy controls, fifteen participants at high risk of developing schizophrenia and three individuals in their first episode of schizophrenia. When type IV was excluded and the hemispheres

were combined, the expression of OFC patterns was compared between the main groups (healthy controls, participants at high risk of developing schizophrenia and patients in their first episode of schizophrenia) and this comparison was found to be significantly different (x^2 = 13.12, df = 4, p = 0.011). In order to identify in which group of participants this finding was most prevalent individuals in their first episode schizophrenia were compared with all other participants. This revealed that the difference in OFC type distribution originates from this group (x^2 = 12.77, df = 2, p = 0.002). The direct comparison of the orbitofrontal type I and type III expression in healthy controls and individuals in their first episode of schizophrenia was also significant: the expression of the orbitofrontal type III was significantly increased in the first episode of schizophrenia group (x^2 = 5.59, df = 1, p = 0.018) while the orbitofrontal type I expression was significantly reduced in the same group (x^2 = 4.47, df = 1, p = 0.034) compared to controls.

Moreover, the distribution of the orbitofrontal patterns on each hemisphere was examined separately. Similar to what was reported by Nakamura and colleagues (2007), the expression of the orbitofrontal types differed significantly between controls, high-risk individuals and patients with schizophrenia on the right hemisphere (x^2 = 9.67, df = 4, p = 0.046), but not on the left hemisphere. When the first episode group was compared with all the other subjects it was revealed that the described above difference originated from the individuals in their first episode of schizophrenia (x^2 = 9.65, df = 2, p = 0.008). When the expression of type III was directly compared in individuals in their first episode of schizophrenia and controls, this revealed a significantly increased frequency of type III in the right hemisphere (x^2 = 4.67, df = 1, p = 0.031) but not in the left. The most important finding was the similarity of the OFC pattern distribution in the high risk subjects who developed schizophrenia to those individuals in their

first episode of schizophrenia: both groups exhibited an increased frequency of type III and reduced frequency of the orbitofrontal type I compared to healthy controls. Moreover, there was a similarity found in the distribution of the orbitofrontal patterns in those high risk individuals who remained well to the distribution of the orbitofrontal patterns in controls. Further, when the high risk individuals who remained well were directly compared to the high risk participants who developed schizophrenia, a significant difference was found in the distribution of the orbitofrontal sulcogyral patterns. When both hemispheres were combined, the OFC type I expression was reduced in those at high risk who went on to develop schizophrenia compared to those at high risk but who remained well ($x^2 = 4.76$, df = 1, p = 0.029). Furthermore, the frequency of the orbitofrontal type III was increased, although this was not significant ($x^2 = 2.65$, df = 1, p = 0.104). An estimated odds ratio (CI) was 2.05 (0.85 – 4.92) when the orbitofrontal type III was present in either hemisphere. In the condition when the orbitofrontal type I was absent from both hemispheres the odds ratio (95% CI) of developing schizophrenia was 2.25 (1.07 – 4.74).

The orbitofrontal type IV was identified in a total of 21 hemispheres (See **Chapters 1** and **3** for more details on this orbitofrontal pattern). This orbitofrontal morphological pattern displayed such features as a connected medial orbital sulcus and a disconnected lateral orbital sulcus. Out of these 21 hemispheres eleven were right hemispheres and 10 were left hemispheres. Unfortunately, there were too few appearances of this pattern in each group to determine whether it can be associated with any condition or illness, or whether it occurs more frequently in one group than in another in the EHRS study.

4.3.3 Gender effect on the distribution of the orbitofrontal morphology

There was significant difference in the distribution of the orbitofrontal type III in the right hemisphere in males (Kruskal - Wallis = 10.182, df = 2, p = 0.006) but not in females (Kruskal - Wallis = 0.673, df = 2, p = 0.714). This suggests that the group difference in distribution of type III in the right hemisphere that was described in 4.3.2 (x^2 = 10.664, df = 2, p = 0.005) might be associated with gender and originated in male participants. Intriguingly, a gender effect was observed on the distribution of the orbitofrontal type III in the left hemisphere as well, but this time it originated in females (Kruskal - Wallis = 5.761, df = 2, p = 0.056) rather than in males (Kruska - Wallis = 3.110, df = 2, p = 0.211), although there was no difference found in the distribution of the orbitofrontal type III in the left hemisphere when both genders were included (x^2 = 4.202, df = 2, p = 0.122).

4.3.4 The symmetry - asymmetry comparison of orbitofrontal morphology between the groups

The scans were considered as symmetric if they contained the same orbitofrontal pattern in the right and in the left hemisphere: type I in the right and type I in the left hemispheres, type II in the right and type II in the left hemispheres, or type III in the right and type III in the left hemispheres. Those scans that contained different orbitofrontal sulcogyral patterns in the right and in the left hemispheres (any other non-symmetric combination) were named asymmetric. Later the distribution of the symmetric and asymmetric scans was compared between the groups and found that this differed significantly (Kruskal - Wallis = 6.674, df = 2, p = 0.036). The following group by group direct comparison revealed that the healthy controls and high risk individuals tended to

be more symmetric (44.4% and 44.2% of symmetric scans respectively) with no difference between the two groups (Kruskal - Wallis = 0.001, df = 1, p = 0.978), while patients with schizophrenia were more asymmetric (11.8% of symmetric scans) and differed from both controls (Kruskal - Wallis = 5.395, df = 1, p = 0.020) and the high risk group (Kruskal - Wallis = 6.512, df = 1, p = 0.011).

4.3.5 Distribution of the cingulate and paracingulate sulcus morphological variants between the main groups

As the cingulate sulcus is always present its morphological variants were examined. An accepted classification of the anterior cingulate morphology is based on the continuity of the CS, that is whether it has a single continuous form or is fragmented into pieces. Then the number of CS pieces was compared between the groups. There was a significant difference found in distribution of the CS pieces between the groups in both the left (Kruskal - Wallis = 15.5, df = 2, p < 0.001) and right (Kruskal - Wallis = 12.7, df = 2, p = 0.002) hemispheres in such a way that the control individuals tended to have a single continuous CS in both hemispheres, while participants at high risk of developing schizophrenia or in their first episode of schizophrenia were more likely to have a 'disconnected' ('broken') CS with 2 or 3 pieces (segments). The following post-hoc Mann - Whitney U test confirmed a significant difference in distribution of the CS pieces between all pairs with the exception of the comparison between the high risk and schizophrenia groups for the right hemisphere (p = 0.104).

Unlike the cingulate sulcus with both males and females included there was no difference found in the distribution of the paracingulate sulcus variants in the right hemisphere (Kruskal - Wallis = 3.251, df = 2, p = 0.197). However, there was a nearly significant difference found in the distribution of the PCS variants in

the left hemisphere (Kruskal - Wallis = 5.679, df = 2, p = 0.058) determined by the prominent PCS in the left hemisphere (Kruskal - Wallis = 6.032, df = 2, p = 0.049). See next section 4.3.6 for further details.

4.3.6 Gender effect on the distribution of the cingulate and paracingulate sulcus morphological variants between the main groups

As there was a gender effect on the orbitofrontal morphology discovered it was important to examine whether the anterior cingulate morphology would have this effect and if so, whether this effect would be similar to the one found for the orbitofrontal morphology. In fact, there was a significant difference found in the distribution of the CS pieces in the left hemisphere in male participants (Kruskal - Wallis = 7.365, df = 2, p = 0.025) unlike in females (Kruskal - Wallis = 0.747, df = 2, p = 0.688). However, female participants differed from males in the distribution of CS pieces in the right hemisphere (Kruskal - Wallis = 10.562, df = 2, p = 0.005 for females, Kruskal - Wallis = 1.192, df = 2, p = 0.551 for males).

Despite absence of any between group differences of the paracingulate morphology in the right hemisphere a gender effect on the distribution of the paracingulate sulcus was examined between the groups in both right and left hemispheres. The direct gender analysis revealed that male control participants had a significantly increased frequency of the prominent PCS in the right hemisphere compared to both high-risk participants (Kruskal - Wallis = 8.925, df = 1, p = 0.003) and patients with schizophrenia (Kruskal - Wallis = 7.136, df = 1, p = 0.008). Moreover, there was a significant difference found in distribution of the prominent PCS in the right hemisphere in female participants with its reduced frequency in patients with schizophrenia compared to both controls (Kruskal - Wallis = 3.677, df = 1, p = 0.055) and the high-risk individuals (Kruskal

- Wallis = 5.895, df = 1, p = 0.015). However, there was no gender effect found on expression of the prominent PCS either in female (Kruskal - Wallis = 2.917, df = 2, p = 0.233) or male (Kruskal - Wallis = 1.254, df = 2, p = 0.534) participants in the left hemisphere.

4.3.7 The symmetry - asymmetry comparison of the cingulate and paracingulate sulcul morphological variants between the groups

For this type of comparison scans were rated as symmetric if they had the same variant of the cingulate sulcus (a single piece only or 'broken' into segments only) in the right and in the left hemispheres. All the other scans were classified as asymmetric. It was discovered that the groups differed significantly in these symmetry-asymmetry scores (Kruskal - Wallis = 6.065, df = 2, p = 0.048). The following direct group by group comparison revealed that this difference originated from the comparison between the healthy control and high risk individuals (Kruskal - Wallis = 4.347, df = 1, p = 0.037), and from the difference between the control and schizophrenia groups (Kruskal - Wallis = 5.384, df = 1, p = 0.020). As in the case of the orbitofrontal symmetry - asymmetry, healthy controls tended to be more symmetric (83.5% of symmetric scans), whereas patients with schizophrenia were more likely to be asymmetric (52.9% of symmetric scans).

In order to examine the PCS symmetry the scans were rated as symmetric if they possessed the same variant of the paracingulate sulcus (absent, present or prominent) in the right and in the left hemisphere. All the other scans were rated as asymmetric. Surprisingly, there was no difference found in the PCS symmetry-asymmetry score between the groups (Kruskal - Wallis = 0.611, df = 2, p = 0.737).

4.3.8 Associations between orbitofrontal and anterior cingulate morphology

Healthy controls

There were no associations found between the orbitofrontal morphological variants and the paracingulate sulcus on the right hemisphere. However, there was a significant association between the orbitofrontal type III pattern in the right hemisphere and the right cingulate sulcus (Kruskal - Wallis = 5.317, df = 1, p = 0.021) in such a way that those healthy individuals with type III in the right hemisphere were more likely to be in a possession of the segmented cingulate sulcus in the right hemisphere compared to those participants that were without the orbitofrontal type III in the right hemisphere. These results were more likely driven by male participants (Kruskal - Wallis = 3.004, df = 1, p = 0.083) rather than by females (Kruskal - Wallis = 2.465, df = 1, p = 0.116).

There was a trend to association found between the orbitofrontal type III in the left hemisphere and the paracingulate sulcus in the female participants (Kruskal - Wallis = 2.912, df = 1, p = 0.088) in a such a way that those with type III were more likely to have the paracingulate sulcus present in the left hemisphere compared to those without the orbitofrontal type III.

The high risk participants

There was a nearly significant association found in female participants between the orbitofrontal type II in the left hemisphere and the left paracingulate sulcus (Kruskal - Wallis = 3.713, df = 1, p = 0.054) in such a way that those with type II in the left hemisphere were less likely to be in a possession of the connected

paracingulate variant compared to those that were without type II. There was a particularly strong association found in male participants between the orbitofrontal morphology and the connected variant of the paracingulate sulcus (Kruskal - Wallis = 9.545, df = 2, p = 0.008) that demonstrated that in males those with the orbitofrontal type III in the left hemisphere were less likely to possess the connected variant of the left paracingulate sulcus compared to males with any other orbitofrontal pattern (Kruskal - Wallis = 8.736, df = 1, p = 0.003 for type III - connected paracingulate sulcus association).

With both genders combined there was an association found between the orbitofrontal type II in the right hemisphere and the presence of the right paracingulate sulcus (Kruskal - Wallis = 4.713, df = 1, p = 0.030) in such a way that those participants with type II in the right hemisphere were more likely to be in a possession of the paracingulate sulcus as well. This difference was more likely to be found in females (Kruskal - Wallis = 5.453, df = 1, p = 0.020), than in males (Kruskal - Wallis = 1.038, df = 1, p = 0.308).

Those with schizophrenia

With both genders combined there was a nearly significant association found between the orbitofrontal type III in the left hemisphere and the connected PCS variant (Kruskal - Wallis = 3.795, df = 1, p = 0.051) in such a way that those participants with type III in the left hemisphere were more likely to be in a possession of the connected version of the PCS as well. This association was more likely to be found in males (Kruskal - Wallis = 6.563, df = 1, p = 0.010), rather than in females (Kruskal - Wallis = 0.400, df = 1, p = 0.527).

With both genders combined there was a nearly significant association found between the orbitofrontal type I in the right hemisphere and the connected PCS variant (Kruskal - Wallis = 3.778, df = 1, p = 0.052) in such a way that those participants with type I in the right hemisphere were more likely to be in a possession of the connected version of the PCS as well. There was no gender effect found on this association.

4.3.9 Association between cingulate and paracingulate sulci

Healthy controls

With both genders combined there was an association found between the right cingulate sulcus and the right (Kruskal - Wallis = 5.645, df = 2, p = 0.059) and left (Kruskal - Wallis = 6.876, df = 2, p = 0.032) paracingulate sulci in healthy controls in such a way that participants with the disconnected right cingulate sulcus were more likely to posses the present variant of the right PCS and an absent left paracingulate sulcus. There was no convincing gender effect found on this association although it is possible that this association is more likely to be found in females (Kruskal - Wallis = 5.175, df = 2, p = 0.075), rather than in males (Kruskal - Wallis = 0.133, df = 1, p = 0.715).

The high risk participants

With both genders combined there was an association found between the left cingulate sulcus and the left paracingulate sulcus in individuals at high risk of developing schizophrenia (Kruskal - Wallis = 7.840, df = 2, p = 0.020) in such a way that participants with the connected cingulate sulcus were more likely to posses the present or prominent variant of the left paracingulate sulcus. This

association was more likely to be found in females (Kruskal - Wallis = 7.121, df = 2, p = 0.028), rather than in males (Kruskal - Wallis = 1.607, df = 1, p = 0.205).

Those with schizophrenia

With both genders combined there was an association found between the left cingulate sulcus and the right paracingulate sulcus in individuals with schizophrenia (Kruskal - Wallis = 4.028, df = 1, p = 0.045) in such a way that participants with the disconnected left cingulate sulcus were more likely to have the right paracingulate sulcus being absent. This association was more likely to be found in males (Kruskal - Wallis = 4.500, df = 1, p = 0.034), rather than in females (Kruskal - Wallis = 0.960, df = 1, p = 0.327).

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4.3.10 Neuropsychological and clinical associations of orbitofrontal morphology

Neuropsychological and clinical associations of the orbitofrontal pattern morphological variants were examined in the high risk participants as they were scanned when they were well. It was considered to be important to analyse whether orbitofrontal morphology on its own or in combination with the anterior cingulate morphological variants might improve the prediction of schizophrenia in the high risk individuals.

4.3.10.1 The RISC scores, SIS factors and the orbitofrontal morphology

The orbitofrontal type III in the right hemisphere

Given that the orbitofrontal type III was previously found to be associated with schizophrenia (Nakamura *et al.,* 2007), it was examined whether the presence of this morphological variant in the high risk participants was associated with scores on the RISC and the SIS factors. There was an association found between the presence of the orbitofrontal type III in either hemisphere and the SIS psychotic symptoms factor rating (t = 2.9, df = 122, p = 0.024), in such a way that the participants with type III had a higher score on this factor. This factor may represent a greater range of symptoms including psychotic–like phenomena, magical thinking and suspiciousness (Miller *et al.,* 2002). Unexpectedly, the association between expression of the orbitofrontal type III in either hemisphere and the score on the RISC was present only at trend level (t = 1.7, df = 128, p = 0.089). Even though, those who possessed type III scored higher on the RISC compared to those who did not.

Then the association was examined between type III in the right or in the left hemisphere separately and the SIS and RISC scores. With both males and females included the orbitofrontal type III in the right hemisphere was found to be associated with the SIS function factor (Kruskal - Wallis = 4.57, df = 1, p = 0.033) in such a way that those with type III in the right hemisphere scored less (mean = - 0.61, SD = 0.84) compared to those high risk participants who were without type III in the right hemisphere (mean = - 0.09, SD = 0.92).

The orbitofrontal type III in the left hemisphere

With both males and females included the orbitofrontal type III in the left hemisphere was found to be associated with the SIS psychotic symptoms factor (Kruskal - Wallis = 4.405, df = 1, p = 0.036) in such a way that those with type III in the left hemisphere scored higher (mean = 0.4, SD = 0.88) compared to those high risk participants who were without type III in the left hemisphere (mean = - 0.1, SD = 0.99).

The orbitofrontal type II in the right hemisphere

With both males and females included the orbitofrontal type II in the right hemisphere was found to be associated with the SIS psychotic symptoms factor (Kruskal - Wallis = 4.389, df = 1, p = 0.036) and the RISC scores (Kruskal - Wallis = 4.762, df = 1, p = 0.029) in such a way that those with type II in the right hemisphere scored less in the SIS psychotic symptoms factor (mean = - 0.39, SD = 1.1) and the RISC scores (mean = 25.47, SD = 12.3) compared to those high risk participants who were without type II in the right hemisphere (mean = 0.08, SD = 0.92 for the SIS psychotic factor and mean = 30.39, SD = 10.1 for the RISC scores).

The orbitofrontal type I in the left hemisphere

With both males and females included the orbitofrontal type I in the left hemisphere was found to be associated with the SIS negative symptoms factor (Kruskal - Wallis = 4.86, df = 1, p = 0.027) in such a way that those with type I in the left hemisphere scored higher (mean = 0.21, SD = 0.75) compared to those

high risk participants who were without type I in the left hemisphere (mean = - 0.24, SD = 1.13).

The orbitofrontal type II in the left hemisphere

With both males and females included the orbitofrontal type II in the left hemisphere was found to be associated with the SIS social functioning factor (Kruskal - Wallis = 6.405, df = 1, p = 0.011) and the SIS negative symptoms factor (Kruskal - Wallis = 7.097, df = 1, p = 0.008) in such a way that those with type II in the left hemisphere scored less in the SIS negative symptoms factor (mean = - 0.44, SD = 1.25) and higher in the SIS social functioning (mean = 0.15, SD = 0.99) compared to those high risk participants who were without type II in the left hemisphere (mean = 0.17, SD = 0.78 for the SIS negative symptoms score and mean = - 0.28, SD = 0.86 for the SIS social functioning).

When only high risk males with type II in the left hemisphere were examined it was discovered that the results on the SIS negative symptoms might come from this group as those male high risk with the type II in the left hemisphere scored less on this factor (mean = - 0.89, SD = 1.37) than those male without (mean = - 0.08, SD = 0.84) (Kruskal - Wallis = 5,151, df = 1, p = 0.023).

4.3.10.2 The Stroop test and orbitofrontal morphology

In order to examine the performance of participants at high genetic risk of developing schizophrenia possessing different orbitofrontal sulcogyral patterns and to consider the gender effect on the orbitofrontal morphology and its associations the gender* orbitofrontal pattern interactions were analysed in the high risk group. A number of associations was found between different

orbitofrontal morphological patterns and the Stroop test performance of the high risk participants. Importantly, at least some of those associations were affected by gender.

The orbitofrontal type I in the right hemisphere

There was a significant type I in the right hemisphere by gender interaction (RH type I * Gender: F = 4.022, df = 3, p = 0.009) found in such a way that male participants at high risk of developing schizophrenia without the orbitofrontal type I in the right hemisphere were significantly slower in a reading of the first list of the Stroop test (mean = 18.955, SD = 26.6752) than females without type I in the right hemisphere (mean = 9.517, SD = 1.01) and slower than both males (mean = 10.008, SD = 1.5979) and females (mean = 10.139, SD = 2.3666) with the orbitofrontal type I in the right hemisphere.

There was a significant type I in the right hemisphere by gender interaction (RH type I * Gender: F = 3.598, df = 3, p = 0.015) found in such a way that male participants at high risk of developing schizophrenia without the orbitofrontal type I in the right hemisphere were reading the second list of the Stroop test significantly more slowly (mean = 21.068, SD = 25.99) than females without type I in the right hemisphere (mean = 12.638, SD = 2.81) and more slowly than both males (mean = 12.85, SD = 2.13) and females (mean = 12.657, SD = 1.964) with the orbitofrontal type I in the right hemisphere.

Moreover, there was a significant type I in the right hemisphere by gender interaction (RH type I * Gender: F = 3.156, df = 3, p = 0.027) found in such a way that male participants at high risk of developing schizophrenia without the orbitofrontal type I in the right hemisphere were reading slower the third list of

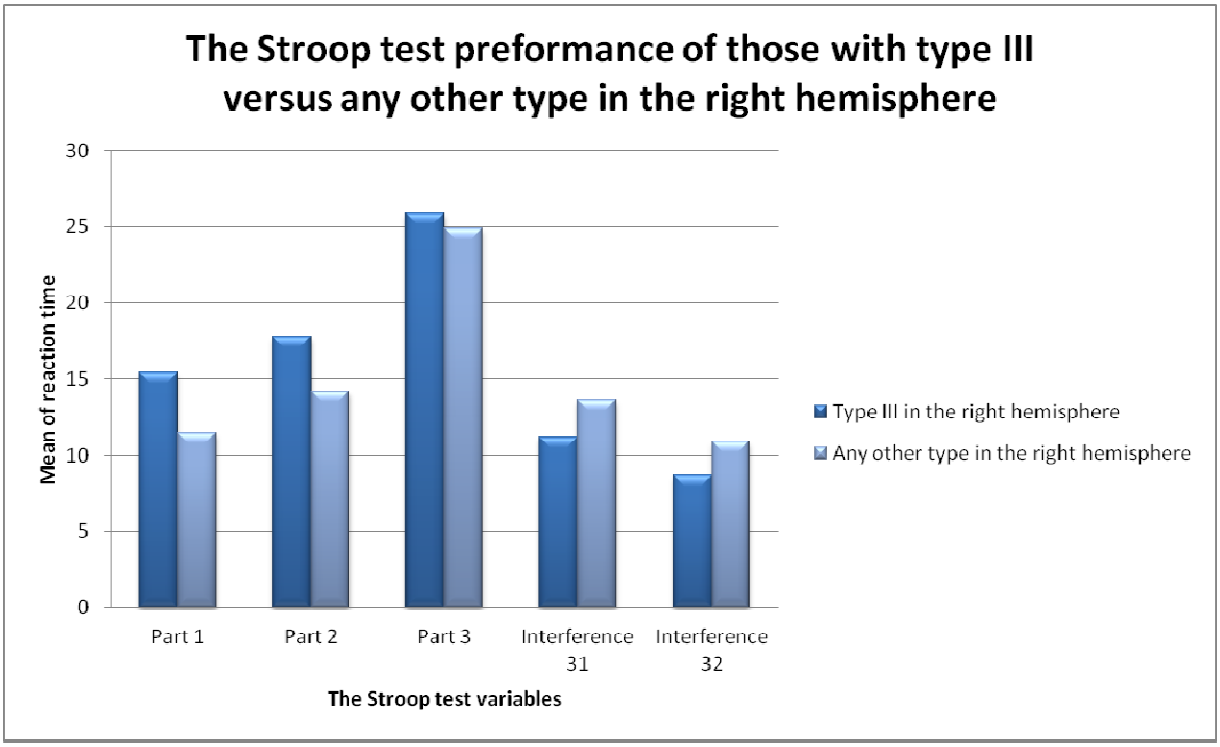
Stroop test (mean = 30.274, SD = 23.47) than females without type I in the right hemisphere (mean = 20.75, SD = 3.89) and slower than both males (mean = 24.991, SD = 5.83) and females (mean = 23.61, SD = 5.66) with the orbitofrontal type I in the right hemisphere.

Furthermore, when interferences were analysed it was discovered that there was a significant type I in the right hemisphere by gender interaction (RH type I * Gender: F = 2.79, df = 3, p = 0.043) in such a way that male participants at high risk with orbitofrontal type I in the right hemisphere showed bigger reaction time differences between reading the first and the third lists of the Stroop test (mean = 14.99, SD = 5.75) than females with type I in the right hemisphere (mean = 13.47, SD = 5.73) and than both males (mean = 12.53, SD = 4.69) and females (mean = 11.23, SD = 3.91) without the orbitofrontal type I in the right hemisphere.

There was a significant type I in the right hemisphere by gender interaction (RH type I * Gender: F = 4.167, df = 3, p = 0.007) found in such a way that male participants at high risk of developing schizophrenia with the orbitofrontal type I in the right hemisphere showed bigger reaction time differences between the reading in the second and the third parts of the Stroop test (mean = 12.14, SD = 4.72) than females with type I in the right hemisphere (mean = 10.95, SD = 4.78) and than both males (mean = 10.19, SD = 4.74) and females (mean = 8.11, SD = 2.89) without the orbitofrontal type I in the right hemisphere.

Overall, the associations between the Stroop reaction times and expression of the orbitofrontal type I in the right hemisphere meant that those at a high risk with type I performed better than participants with any other type in the right hemisphere.

Figure 4.3. The Stroop test performance of those with the orbitofrontal type III versus any other orbitofrontal pattern in the right hemisphere with both genders combined.



Part 1 = reaction time recorded during the part 1 of the test

Part 2 = reaction time recorded during the second part of the test

Part 3 = reaction time during the third part of the test

Interference 31 = the differences in the reaction times recorded during the parts 1 and 3 of the Stroop test

Interference 32 = the differences in the reaction times recorded during the parts 2 and 3 of the Stroop test

The orbitofrontal type III in the right hemisphere (See Figure 4.3)

When performance of the participants with the orbitofrontal type III in the right hemisphere was analysed it was discovered that there was a nearly significant type III in the right hemisphere by gender interaction (RH type III * Gender: F = 2.476, df = 3, p = 0.064) in such a way that male participants at high risk of developing schizophrenia with the orbitofrontal type III in the right hemisphere were slower while performing in the third part of the Stroop test (mean = 31.922, SD = 25.798) than females with type III in the right hemisphere (mean = 19.125, SD = 2.035) and slower than both males (mean = 26.653, SD = 14.582) and females (mean = 23.063, SD = 5.39) without the orbitofrontal type III in the right hemisphere.

Further, there was a trend to significance found for type III in the right hemisphere by gender interaction (RH type III * Gender: F = 2.32, df = 3, p = 0.078) in such a way that male participants at high risk of developing schizophrenia without the orbitofrontal type III in the right hemisphere showed bigger reaction time differences between reading the second and the third parts of the Stroop test (mean = 11.486, SD = 4.6342) than females without type III in the right hemisphere (mean = 10.317, SD = 4.5263) and than both males (mean = 10.138, SD = 6.0408) and females (mean = 7.200, SD = 1.7889) with the orbitofrontal type III in the right hemisphere.

The orbitofrontal type I in the left hemisphere

It was discovered that there was a significant type I in the left hemisphere by gender interaction (LH type I * Gender: F = 2.771, df = 3, p = 0.044) in such a way that male participants at high risk of developing schizophrenia without the

orbitofrontal type I in the left hemisphere were slower while performing the first part of the Stroop test (mean = 17.1, SD = 24.3233) than females without type I in the left hemisphere (mean = 9.758, SD = 2.0306) and slower than both males (mean = 10.253, SD = 1.9848) and females (mean = 10.071, SD = 2.0051) with the orbitofrontal type I in the left hemisphere.

It was found that there was a significant type I in the left hemisphere by gender interaction (LH type I * Gender: F = 3.07, df = 3, p = 0.030) in such a way that male participants at high risk of developing schizophrenia without the orbitofrontal type I in the left hemisphere were slower while performing the second part of the Stroop test (mean = 19.816, SD = 23.5684) than females without type I in the left hemisphere (mean = 13.161, SD = 2.7306) and slower than both males (mean = 12.544, SD = 2.0413) and females (mean = 12.169, SD = 1.644) with the orbitofrontal type I in the left hemisphere.

It was discovered that there was a significant type I in the left hemisphere by gender interaction (LH type I * Gender: F = 4.028, df = 3, p = 0.009) in such a way that male participants at high risk of developing schizophrenia without the orbitofrontal type I in the left hemisphere were slower while performing the third part of the Stroop test (mean = 30.633, SD = 21.0684) than females without type I in the left hemisphere (mean = 23.503, SD = 5.3702) and slower than both males (mean = 23.409, SD = 5.5934) and females (mean = 21.749, SD = 5.0806) with the orbitofrontal type I in the left hemisphere.

The orbitofrontal type II in the left hemisphere

It was found that there was a trend towards significance for the orbitofrontal type II in the left hemisphere by gender interaction (LH type II * Gender: F = 2.385, df

= 3, p = 0.072) in such a way that male participants at high risk of developing schizophrenia with the orbitofrontal type II in the left hemisphere were slower while performing the second part of the Stroop test (mean = 20.588, SD = 24.2165) than females with type II in the left hemisphere (mean = 13.447, SD = 3.0909) and slower than both males (mean = 14.354, SD = 12.9095) and females (mean = 12.341, SD = 1.817) without the orbitofrontal type II in the left hemisphere.

It was discovered that there was a significant type II in the left hemisphere by gender interaction (LH type II * Gender: F = 3.69, df = 3, p = 0.014) in such a way that male participants at high risk of developing schizophrenia with the orbitofrontal type II in the left hemisphere were slower while performing the third part of the Stroop test (mean = 31.932, SD = 21.1546) than females with type II in the left hemisphere (mean = 24.0, SD = 5.8069) and slower than both males (mean = 24.93, SD = 12.6789) and females (mean = 22.057, SD = 4.9877) without the orbitofrontal type II in the left hemisphere.

It was found that there was a significant type II in the left hemisphere by gender interaction (LH type II * Gender: F = 3.306, df = 3, p = 0.022) in such a way that male participants at high risk of developing schizophrenia with the orbitofrontal type II in the left hemisphere showed bigger reaction time differences between the reading in the first and the third parts of the Stroop test (mean = 15.625, SD = 4.8451) than females with type II in the left hemisphere (mean = 14.853, SD = 5.1032) and higher than both males (mean = 13.144, SD = 5.5648) and females (mean = 11.839, SD = 5.0989) without the orbitofrontal type II in the left hemisphere.

4.3.10.3 The Rey Auditory Verbal Learning Test and orbitofrontal sulcogyral patterns

The orbitofrontal type III in the right hemisphere

As it was considered to be important to examine a gender effect on any association between brain structure and neuropsychological scores, the orbitofrontal patterns by gender interactions were investigated using structural and neuropsychological scores as a dependent variable for every participant at the high risk group. For the Rey Auditory Verbal Learning Test it was found that there was the type III orbitofrontal pattern in the right hemisphere by gender interaction with the total number of words recalled following interference (postdistractor trial or trial 6) as a dependent variable (RH type III * Gender: $F = 3.832$, $df = 3$, $p = 0.011$) in such a way that the female high risk participants with type III in the right hemisphere scored significantly less or recalled less words during the postdistractor trial (mean = 9.57, SD = 2.225) compared to both females without type III (mean = 11.69, SD = 2.4) and male participants with (mean = 11.00, SD = 1.803) or without the orbitofrontal type III in the right hemisphere (mean = 10.24, SD = 2.809).

4.3.10.4 The brain volume and the orbitofrontal morphology

In **Chapter 6** it will be examined whether there are associations between orbitofrontal morphology and grey and white matter density using Voxel - Based Morphology technique in healthy controls. In this chapter associations between brain volume and orbitofrontal morphology were investigated. Given that different participants were used in **Chapter 6**, it is important to know whether the

same associations could be replicated in various studies with different participants.

The orbitofrontal type I in the right hemisphere

It was discovered that there was a significant type I in the right hemisphere by gender interaction (RH type I * Gender: $F = 16.184$, $df = 3$, $p < 0.0001$) in such a way that male participants at high risk without orbitofrontal type I in the right hemisphere had larger volume of the right temporal lobe (mean = 89307.7, SD = 7124.54) than females without type I in the right hemisphere (mean = 77563.98, SD = 7213.85) and larger than both males (mean = 84281.72, SD = 10819.79) and females (mean = 77938.61, SD = 6438.71) with the orbitofrontal type I in the right hemisphere.

Moreover, there was a significant type I in the right hemisphere by gender interaction found (RH type I * Gender: $F = 5.299$, $df = 3$, $p = 0.002$) in such a way that male participants at high risk with orbitofrontal type I in the right hemisphere had larger volume of the right caudate nucleus (mean = 4766.13, SD = 677.67) than females with type I in the right hemisphere (mean = 4267.66, SD = 571.39) and larger than both males (mean = 4741.06, SD = 691.11) and females (mean = 4593.82, SD = 723.1) without the orbitofrontal type I in the right hemisphere.

The orbitofrontal type II in the right hemisphere

There was a significant type II in the right hemisphere by gender interaction found (RH type II * Gender: $F = 9.271$, $df = 3$, $p < 0.0001$) in such a way that male participants at high risk without orbitofrontal type II in the right hemisphere

had larger volume of the right frontal lobe (mean = 84210.33, SD = 12533.51) than females without type II in the right hemisphere (mean = 73372.24, SD = 10883.39) and larger than both males (mean = 83589.81, SD = 10332.01) and females (mean = 81252.22, SD = 13348.1) with the orbitofrontal type II in the right hemisphere.

Moreover, there was a significant type II in the right hemisphere by gender interaction found (RH type II * Gender: $F = 26.413$, $df = 3$, $p < 0.0001$) in such a way that male participants at high risk with orbitofrontal type II in the right hemisphere had larger volume of the left temporal lobe (mean = 87933.37, SD = 6885.1) than females with type II in the right hemisphere (mean = 75152.85, SD = 8003.77) and larger than both males (mean = 84358.49, SD = 8266.01) and females (mean = 74737.17, SD = 6394.6) without the orbitofrontal type II in the right hemisphere.

Furthermore, it was discovered that there was a significant type II in the right hemisphere by gender interaction (RH type II * Gender: $F = 8.395$, $df = 3$, $p < 0.0001$) in such a way that male participants at high genetic risk of developing schizophrenia with the orbitofrontal type II in the right hemisphere had larger volume of the left amygdala-hippocampal complex (mean = 4786.76, SD = 456.24) than females with type II in the right hemisphere (mean = 4518.22, SD = 576.76) and larger than both males (mean = 4748.44, SD = 642.1) and females (mean = 4301.42, SD = 403.31) without the orbitofrontal type II in the right hemisphere.

The orbitofrontal type III in the right hemisphere

There was a significant type III in the right hemisphere by gender interaction found (RH type III * Gender: F = 5.104, df = 3, p = 0.002) in such a way that male participants at high genetic risk of developing schizophrenia without orbitofrontal type III in the right hemisphere had larger volume of the right caudate nucleus (mean = 4802.34, SD = 709.66) than females without type III in the right hemisphere (mean = 4357.32, SD = 660.65) and larger than both males (mean = 4412.73, SD = 171.14) and females (mean = 4569.64, SD = 460.77) with the orbitofrontal type III in the right hemisphere.

The orbitofrontal type III in the left hemisphere

There was a significant type III in the left hemisphere by gender interaction found (RH type I * Gender: F = 12.193, df = 3, p < 0.0001) in such a way that male participants at high risk of developing schizophrenia with orbitofrontal type III in the left hemisphere had larger volume of the left thalamic nucleus (mean = 7004.14, SD = 923.68) than females with type III in the left hemisphere (mean = 5888.48, SD = 507.38) and larger than both males (mean = 6449.48, SD = 736.08) and females without the orbitofrontal type III in the left hemisphere (mean = 5892.53, SD = 643.56).

4.3.10.5 Fronto - parietal connectivity and orbitofrontal morphology

The orbitofrontal type III in the right hemisphere

With both males and females included individuals at high risk of developing schizophrenia who had the orbitofrontal type III in the right hemisphere had

increased fronto-parietal connectivity (mean = 1.24, SD = 0.44) compared to those without (mean = 0.75, SD = 0.61) (Kruskal - Wallis = 4.309, df = 1, p = 0.038). This result might be associated with females (Kruskal - Wallis = 3.441, df = 1, p = 0.064) in such a way that those female participants with the orbitofrontal type III in the right hemisphere had an increased fronto-parietal connectivity (mean = 1.38, SD = 0.42) compared to those females without (mean = 0.85, SD = 0.52) (type III in the right hemisphere by gender interaction: F = 2.298, df = 3, p = 0.086).

The orbitofrontal type II in the left hemisphere

Male high risk participants with the orbitofrontal type II in the left hemisphere had an increased fronto - parietal connectivity (mean = 1.29, SD = 0.79) compared to those males without (mean = 0.5, SD = 0.57) (Kruskal - Wallis = 4.590, df = 1, p = 0.032). To support this, it was discovered that there was a type II in the left hemisphere by gender interaction (LH type II * Gender: F = 7.353, df = 3, p = 0.009) when the fronto - parietal connectivity was entered as a dependent variable. This interaction was in such a way that male participants with orbitofrontal type II in the left hemisphere had increased fronto-parietal connectivity (mean = 1.3, SD = 0.7) compared to males with any other type in the left hemisphere (mean = 0.5, SD = 0.6), or female participants with (mean = 0.8, SD = 0.5) or without (mean = 0.9, SD = 0.5) type II in the left hemisphere.

4.3.11 Positive and negative predictive values and sensitivity of the orbitofrontal morphology alone and in combination with the paracingulate variants

It was considered to be important to calculate the positive and negative predictive values, as well as sensitivity and specificity evaluating those conditions when one or both following structural markers in one subject were identified: the right orbitofrontal sulcogyral pattern type III and/or the left prominent paracingulate variant. The orbitofrontal type III in the right hemisphere and the left prominent paracingulate sulcus were chosen for this analysis as the distributions of both these markers were found to be altered in participants with schizophrenia. These values were estimated in those at high genetic risk of developing schizophrenia.

The positive predictive value in this case was proportion of participants at high risk with the right orbitofrontal type III and/or the left prominent PCS who developed schizophrenia.

The negative predictive value was proportion of those participants at high risk without type III in the right hemisphere and/or the left prominent PCS who remained well.

Sensitivity in this case was the probability that presence of the right orbitofrontal type III and/or the left prominent PCS will indicate schizophrenia among those with schizophrenia.

Specificity is the fraction of those without schizophrenia who will not have the right orbitofrontal type III and/or the left prominent PCS.

4.3.11.1 The orbitofrontal type III in the right hemisphere:

	Schizophrenia present	Schizophrenia absent
Type III present	4	13
Type III absent	13	116

Positive predictive value = 4 / (4 +13) * 100 = 23.5%

Negative predictive value = 116 / (13 + 116) * 100 = 89.9%

Sensitivity = 4 / (4 + 13) * 100 = 23.5%

Specificity = 116 / (116 + 13) * 100 = 89.9%

4.3.11.2 The left prominent PCS:

	Schizophrenia present	Schizophrenia absent
Left PCS present	12	58
Left PCS absent	5	71

Positive predictive value = 12/(12 + 58) * 100 = 17.2%

Negative predictive value = 71/(5 + 71) * 100 = 93.4%

Sensitivity = 12/ (12 +5) * 100 = 70.6%

Specificity = 71 / (71 + 58) = 55.1%

4.3.11.3 Present either type III in the right hemisphere or the left prominent PCS or both of them:

It was considered to be important to examine whether combination of both distinctive features – the right orbitofrontal type III and the left prominent PCS – will influence positive and negative predictive values, as well as sensitivity and

specificity. If this is the case then it might support the idea of combining these structural features into the system of markers to increase prediction of schizophrenia in high risk individuals.

	Schizophrenia present	Schizophrenia absent
Type III or left PCS or both present	14	71
Type III or left PCS or both absent	3	58

Positive predictive value = 14 / (14 + 71) * 100 = 17.5%

Negative predictive value = 58 / (3 + 58) * 100 = 95.5%

Sensitivity = 14 / (14 + 3) * 100 = 82.4%

Specificity = 58 / (58 + 71) * 100 = 48.8%

4.4 Discussion

In this chapter orbitofrontal morphology and its association with the paracingulate sulcus, the symmetry - asymmetry scores and gender effect on the orbitofrontal and anterior cingulate morphology were examined in the Edinburgh High Risk Study. Neuropsychological scores, associations of the orbitofrontal sulcogyral patterns with brain volume, positive and negative predictive values and sensitivity tests were analysed in those at high risk of developing schizophrenia.

Orbitofrontal cortex

The distribution of the orbitofrontal sulcogyral patterns in healthy controls and individuals in their first episode of schizophrenia was similar to those of adult controls and patients with schizophrenia in the Psychosis Study (See **Chapter 3** for details). There was an increased expression of the orbitofrontal type III and the reduced expression of the orbitofrontal type I found in the right hemisphere in the first episode of schizophrenia. The most important finding was the similarity of the OFC pattern distribution in the high risk subjects who developed schizophrenia to those individuals in their first episode of schizophrenia: both groups exhibited an increased frequency of type III and reduced frequency of the orbitofrontal type I compared to healthy controls. Moreover, there was a similarity in the distribution of the orbitofrontal patterns in those high risk individuals who remained well to the distribution of the orbitofrontal patterns in controls. Further, when a direct comparison was made between the high risk individuals who remained well and the high risk participants who developed schizophrenia, a significant difference was found in the distribution of the orbitofrontal sulcogyral patterns with an increased frequency of type III and

reduced frequency of type I in the right hemisphere in those high risk participants who developed schizophrenia. This data suggest that a particular orbitofrontal sulcogyral pattern, type III, is associated with the development of schizophrenia. On the contrary, people with type I have a reduced risk of this illness.

Similarly to the analysis in **Chapter 3**, a gender effect was examined in the EHRS. As in the Psychosis study, the differences in the distribution of the orbitofrontal type III in the right hemisphere seemed to be originated in males while the distribution of the orbitofrontal type III in the left hemisphere was more likely to be originated in females. Moreover, similarly to the findings in the Psychosis Study healthy controls and high risk individuals tended to be more symmetric (44.4% and 44.2% of symmetric scans respectively) with no difference between the two groups, while patients with schizophrenia were more asymmetric (11.8% of symmetric scans) and differed from both controls and the high risk group of developing schizophrenia.

Anterior Cingulate Cortex

Comparison of the ACC distribution between the groups revealed that the control individuals tended to have a single continuous CS in both hemispheres, while participants at high risk of developing schizophrenia or in their first episode of schizophrenia were more likely to have a 'disconnected' ('broken') CS with 2 or 3 pieces (segments). There was a gender effect found on the distribution of the cingulate sulcus that was similar to one described in **Chapter 3**. The distribution of the cingulate sulcus pieces in the left hemisphere was more likely to be associated with male participants while female participants differed from males in the distribution of the cingulate sulcus pieces in the right hemisphere.

The distribution of the paracingulate sulcus variants in the left hemisphere differed between the groups by the prominent paracingulate sulcus variant in the left hemisphere. The direct gender analysis revealed that male control participants had a significantly increased frequency of the prominent PCS variant in the right hemisphere compared to both high-risk participants and patients with schizophrenia. It is noticeable that the paracingulate sulcus is likely to share the same gender effect as the orbitofrontal morphology in the EHRS as well as in the Psychosis Study (See **Chapter 3** for details).

Similar to the case of the orbitofrontal symmetry – asymmetry in this chapter as well as in **Chapter 3**, healthy controls tended to be more symmetric (83.5% of symmetric scans), whereas patients with schizophrenia were more likely to be asymmetric (52.9% of symmetric scans).

Associations between OFC and ACC

There was a number of associations found in this data between the orbitofrontal and anterior cingulate morphology in the right and left hemispheres. For example, healthy individuals with type III in the right hemisphere were more likely to be in a possession of the segmented cingulate sulcus in the right hemisphere compared to those participants that were without the orbitofrontal type III in the right hemisphere. These results were more likely to be driven by male participants rather than by females (the same gender effect as for the distribution of the orbitofrontal sulcogyral patterns). Further, the high risk males with the orbitofrontal type III in the left hemisphere were less likely to possess the connected variant of the left paracingulate sulcus compared to the high risk males with any other orbitofrontal pattern. Furthermore, those high risk participants with type II in the right hemisphere were more likely to be in a

possession of the paracingulate sulcus as well. This difference was more likely to be found in females than in males. Moreover, those participants with schizophrenia with type III in the left hemisphere were more likely to be in a possession of the connected version of the PCS as well. It was discovered that this association is more likely to be originated in males rather than in females.

Associations between cingulate and paracingulate sulcus were found either in the same hemisphere (between the left connected cingulate sulcus and the left present or prominent paracingulate sulcus in those at high risk of developing schizophrenia, originated in females), or between the opposite hemispheres (the left disconnected cingulate sulcus and the right paracingulate sulcus in patients with schizophrenia, originated in males).

Neuropsychological and clinical associations of the orbitofrontal cortex

There was an association found between the presence of the orbitofrontal type III in either hemisphere and the SIS psychotic symptoms factor rating in such a way that the participants with type III had a higher score on this factor. With both males and females included the orbitofrontal type III in the left hemisphere was found to be associated with the higher scores on the SIS psychotic symptoms factor compared to those high risk participants who were without type III in the left hemisphere. Further, the orbitofrontal type II in the right hemisphere was found to be associated with the SIS psychotic symptoms factor and the RISC scores in such a way that those with type II in the right hemisphere scored less in the SIS psychotic symptoms factor and the RISC scores compared to those high risk participants who were without type II in the right hemisphere. The orbitofrontal type I in the left hemisphere was found to be associated with the SIS negative symptoms factor in such a way that those with type I in the left

hemisphere scored higher compared to those high risk participants who were without type I in the left hemisphere. The orbitofrontal type II in the left hemisphere was found to be associated with the SIS social functioning factor and the SIS negative symptoms factor in such a way that those with type II in the left hemisphere scored less in the SIS negative symptoms factor and higher in the SIS social functioning compared to those high risk participants who were without type II in the left hemisphere. The association between type II in the left hemisphere and the SIS negative symptoms was more likely to be originated in males.

These results suggest that the orbitofrontal patterns may vary in their features. For example, type III in either hemisphere is associated with psychotic symptoms, while type II is less psychotic and is associated with social functioning. This is especially important considering the possibility that the orbitofrontal type II could be related to autism (see **Chapter 8** for details).

The associations between the orbitofrontal sulcogyral patterns and the performance during the Stroop test were also analysed. Those at a high risk of developing schizophrenia with type I in the right hemisphere performed better than participants with any other type. In a contrary, the male participants at high risk of developing schizophrenia with the orbitofrontal type III in the right hemisphere performed poorly in the Stroop test. There is a striking consistency in a way that these orbitofrontal sulcogyral patterns tend to be associated with verbal tests including the Stroop Test in the EHRS, and WASI verbal IQ and the Hayling Sentence Completion Test in the Psychosis Study (see **Chapter 3** for details) with the orbitofrontal type III probably expressing a certain degree of difficulties with inhibitory control to stop and switch the verbal domain. Supporting this, the female high risk participants with type III in the right

hemisphere scored significantly less or recalled fewer words during the postdistractor trial of the Rey Auditory Verbal Learning Test.

The orbitofrontal patterns were also found to be associated with volumes of various brain regions. For example, the male participants at high risk of developing schizophrenia without orbitofrontal type I in the right hemisphere had larger volume of the right temporal lobe and smaller volume of the right caudate nucleus. Further, the male participants at high risk of developing schizophrenia with the orbitofrontal type II in the right hemisphere had smaller volume of the right frontal lobe, larger volume of the left temporal lobe and larger volume of the left amygdala - hippocampal complex. The male participants at high genetic risk of developing schizophrenia with the orbitofrontal type III in the right hemisphere had smaller volume of the right caudate nucleus, while the male participants at high risk of developing schizophrenia with the orbitofrontal type III in the left hemisphere had larger volume of the left thalamic nucleus. These findings show associations between orbitofrontal patterns and volumes of the brain regions that represent parts of the orbitofrontal network. Moreover, it becomes clearer that the same orbitofrontal patterns in the left and right hemisphere might have different characteristics.

Associations between the orbitofrontal sulcogyral patterns and fronto – parietal connectivity were examined. It was discovered that those individuals at high risk of developing schizophrenia who had the orbitofrontal type III in the right hemisphere had increased fronto-parietal connectivity compared to those without. This result might be associated with females rather than males. Further, the male participants at high risk of developing schizophrenia with the orbitofrontal type II in the left hemisphere had an increased fronto - parietal connectivity compared to those males without. These findings suggest that both

orbitofrontal type II and type III are characterised by pathological associations. This is particularly important considering that type III is associated with schizophrenia, while type II might be related to autism (see **Chapter 8** for details).

The calculated negative predictive value for the orbitofrontal type III in the right hemisphere was 89.9%. The calculated negative predictive value for the prominent paracingulate sulcus variant in the left hemisphere was 93.4%. Combination of both the orbitofrontal type III in the right hemisphere and the left prominent paracingulate sulcus variant resulted in the increased negative predictive value 95.5%. These findings may demonstrate importance of the orbitofrontal sulcogyral patterns and the paracingulate sulcus for predictability of the schizophrenia development in the high risk population.

The results of this chapter together with findings from the other chapters contributed to the development of the theory of predictive associations of the orbitofrontal sulcogyral patterns that is formulated and discussed in **Chapter 8** of this thesis.

Orbitofrontal sulcogyral morphology: its distribution, structural and functional associations, and predictive value in different diagnostic groups

The theory of predictive associations of the orbitofrontal sulcogyral patterns

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Chapter 5

Distribution and functional associations of the orbitofrontal morphology in participants at high genetic risk of developing bipolar affective disorder as well as associations between orbitofrontal sulcogyral patterns and anterior cingulate morphology

In this chapter the following is analyzed: the distribution of the orbitofrontal sulcogyral patterns and its associations with the paracingulate sulcus, brain volume and neuropsychological scores in the Bipolar Family Study. The orbitofrontal morphology was assessed in a similar way to the analysis that was performed using data from the Edinburgh High Risk Study (**Chapter 4**). This was supposed to assist in identifying those features of the orbitofrontal morphological sulcogyral patterns that are similar in both cohorts and therefore replicable and most likely will be rather features of the orbitofrontal patterns themselves than those of mental illness. Similarly to previous **Chapters 3** and **4**, the data on the symmetry - asymmetry scores of both orbitofrontal and anterior cingulate morphology, gender effect on the orbitofrontal and cingulate morphology, positive and negative predictive values, and sensitivity tests were included.

5.1 Introduction

The orbitofrontal sulcogyral patterns known as type I, II, III and IV (Chiavaras and Petrides, 2000; Chakirova *et al.,* 2010) were previously found altered in patients with schizophrenia and were represented by the reduction of the orbitofrontal type I and an increased frequency of type III in the right hemisphere (Nakamura *et al.,* 2007). Those patterns were found to be present before schizophrenia is manifested and were associated with psychotic features (Chakirova *et al.,* 2010) even in the pre-morbid state. The early formation of the orbital sulci and the beginning of formation of cerebral pathways in the 3rd trimester of pregnancy (Chi *et al.,* 1977; Kostovic and Jovanov - Milosevic, 2006) suggests that the shaping of the orbitofrontal sulcogyral patterns might reflect such processes as neuronal migration, local neuronal connection, synaptic development, lamination, formation of cytoarchitecture (Rakic, 1988; Armstrong *et al.,* 1995) and is likely to be exposed to multiple genetic (and possibly environmental) influences (Gurling *et al.,* 2006). Given the structure, function, neurotransmitter system and connections within the brain (Mesulam and Mufson, 1982; Morecraft *et al.,* 1992; Van Hoesen *et al.,* 1993; Carmichael and Price, 1994; Petrides and Pandya, 1994; Ongur and Price, 2000; Kringelbach and Rolls, 2004; Walton *et al.,* 2004; Kringelbach, 2005; Fujiwara *et al.,* 2008), the orbitofrontal cortex might be one of the most important areas to look at in the search for a structural pattern that might help to enhance the accuracy of prediction of bipolar disorder in genetically high - risk families.

Moreover, both orbitofrontal and paracingulate sulci are formed at about the same period of gestation while cingulate sulcus is developing earlier around 20th ontogenic week (Chi *et al.,* 1977; Armstrong *et al.,* 1995). This suggests that the orbitofrontal and paracingulate sulci might be influenced by the same environmental and genetic factors. These two factors - the formation of the orbital and paracingulate sulci at the same period of time and possibility to be

affected by similar factors - might justify the search for associations between these two regions. Being developed during such early period these sulci do not change their shape later. Given this, the combination of the orbitofrontal patterns and the paracingulate sulcus could be applied as a marker to predict psychosis.

With regards to an application in psychiatry, a marker is an objective and carefully measured characteristic that can identify individuals from the high risk population who will subsequently develop mental illness. Structural variations of the orbitofrontal and paracingulate morphology might represent a possible objective anatomical measure that could reflect aberrant neurodevelopment and be used to detect bipolar disorder pre-morbidly. However, there were no publications so far on whether both orbitofrontal and paracingulate sulci represent a part of the predictive system that could potentially estimate likelihood of the development of mental illnesses. This is why in this chapter it was attempted to establish whether the orbitofrontal sulcogyral patterns in combination with paracingulate variants might predict the development of depression/bipolar disorder. In order to achieve this the distribution of orbitofrontal patterns, their neuropsychological and clinical associations, the associations between orbitofrontal patterns and anterior cingulate morphology, and the predictive value of those associations in individuals at high genetic risk of developing bipolar disorder were examined.

5.2 Methods

5.2.1 Participants

Participants for this study were recruited as a part of the large and longitudinal Bipolar Family Study, intended to investigate and to follow up those at high genetic risk of developing bipolar disorder. Firstly, patients with a clinical diagnosis of bipolar I disorder were identified from the case loads of psychiatrists across Scotland. Each affected individual was asked to identify their first or second degree relatives aged between 16 and 25 years and to consent to either a review of their case notes, or to a structural clinical interview. The OPCRIT symptom checklist or the structural clinical interview for DSM - IV (SCID) was used to confirm the diagnosis of all affected subjects (McGuffin *et al.,* 1991). The identified unaffected relatives of patients with bipolar I disorder were then invited to participate in the study. Only one unaffected relative was included to the study from the family of each bipolar disorder proband. Unaffected, unrelated control subjects with no personal or family history of bipolar disorder were recruited from the social networks of the high - risk subjects. The high - risk group and controls were matched on age, gender and premorbid IQ. Exclusion criteria for all participants were a personal history of major depression, mania or hypomania, any major neurological disorder, a history of substance dependence, a history of learning disabilities or any history of head injury that included loss of consciousness and also any other contraindications to MRI examination. All participants signed written informed concern. The study was approved by committee A of the Multicentre Regional Ethics Committee for Scotland. Later four volunteers from the healthy control group and twenty four participants from the high risk group were diagnosed with major depressive or bipolar affective disorder. Individuals from the healthy controls group who became ill were removed from further analysis. The high - risk group was subdivided into those who remained well and those who became ill.

5.2.2 Clinical assessment

The lifetime absence of affective disorders, schizoaffective disorder and schizophrenia was confirmed by a trained psychiatrist who interviewed all participants using the structured clinical interview for DSM - IV (SCID). The Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HDRS) were used to rate the current manic and depressive symptoms. The presence or absence of positive, negative and general psychopathological symptoms was assessed using the Positive and Negative Symptom Scale (PANSS). Clinical data was available for 66 controls and 107 high risk individuals. Additionally, there was also obtained detailed information about lifetime alcohol and drug use.

The Temperament Evaluation of Memphis, Pisa, Paris and San Diego - autoquestionnaire (TEMPS - A) was used to assess estimates of temperamental variations in minor affective symptoms (Akiskal *et al.,* 2005 a, b). The TEMPS-A is a validated self - rated questionnaire that provides measures of depressive, cyclothymic, hyperthymic, anxious and irritable temperament.

All clinical assessments were conducted prior or immediately scanning.

5.2.3 Neuropsychological examination

A battery of neuropsychological tests was applied to examine such cognitive functions as attention, memory and executive functioning. Memory and verbal learning ability was assessed using the California Verbal Learning Test (CVLT) and the Logical Memory subtest from the Wechsler Memory Scale – III (WMS – III).

5.2.3.1 The IDED task

The intra – dimensional / extra - dimensional (ID/ED) set - shifting task of the Cambridge Neuropsychological Test Automated Battery (CANTAB) is a neuropsychological test that examines the ability to shift attention between different dimensions or between different stimuli within the same dimension. This task is computerized and it consists of nine stages, including simple discrimination; simple discrimination reversal; compound discrimination; compound discrimination reversal; intra - dimensional shift; intra - dimensional reversal; extra - dimensional shift; extra - dimensional reversal.

At each stage during the task two pairs of superimposed stimuli were presented. The stimuli were solid shapes and lines. Participants were required to identify which of the four stimuli was a target. After every choice they would receive a feedback (positive feedback with a word 'correct' or negative feedback with a word 'incorrect'). When the target was identified (followed by the positive feedback) participants were asked to continue to choose the target until the stimuli would changed or till the target would change. After six consecutive correct responses (six positive feedbacks) the task would proceed to the next stage (the set change or the target change). If the participant was unable to reach the criteria (six consecutive responses) after 50 trials, on any stage, the IDED task would end. Participants were asked to make choice and respond as quickly and accurately as they possibly could.

This task allowed analysing a number of attempted trials and errors during each stage as well as the reaction time. Reversal stages were defined as a reversal of contingencies, where the stimulus that was previously defined as a target became irrelevant and the stimulus which was previously irrelevant became a target. Extra - dimensional shifts were characterized as the shifting

of attention from the stimulus of one dimension to the stimulus of the other dimension (from a solid shape to a line).

5.2.3.2 The NEO-FFI questionnaire

The shortened version of the Neuroticism – Extroversion - Openness Five - Factor Inventory (NEO - FFI) is a 60 - item psychological personality questionnaire which provides an accurate, quick and reliable measure of personality and assisting in understanding of the basic emotional, attitudinal, motivational, interpersonal and experiential styles of each participant in the study. The main five factors of personality measured by the NEO - FFI include:

- Neuroticism (a tendency to experience such unpleasant emotions as anxiety, depression or anger easily),
- Extraversion (a tendency to seek energy, positive emotions and stimulation in the company of others),
- Openness to experience (curiosity and appreciation for adventure, unusual ideas and variety of experience),
- Agreeableness (a tendency to feel compassionate towards others),
- Conscientiousness (a tendency to be dutiful, self-disciplined, motivated for achievements, to demonstrate planned behaviour).

This test was designed to take 10-15 minutes.

5.2.3.3 The Hayling Sentence Completion Task

Immediately after scanning the participants were given the same sequence of sentences on paper as they were provided with when they were under the scanner. Participants were requested to complete each sentence with the word they first thought of in the scanner. Word appropriateness scores were

determined from the list of completion norms (Bloom and Fischler, 1980) which provided probabilities of possible responses. Mean word appropriateness scores and reaction times were calculated in order to compare performance across genotype groups. The detailed description of this task is in **Chapter 7** of this thesis.

5.2.4 Scanning procedure

The scanning procedure was carried out at the Scottish Brain Imaging Research Centre on a GE 1.5 - T Signa scanner (GE Medical, Milwaukee, Wisconsin).

The structural imaging protocol. Midline sagittal localization was followed by two further sequences to image the whole brain. The first sequence was a transverse spin - echo scan, which acquired both T_2- and proton density – weighted images of the brain for clinical reporting by a consultant neuroradiologist. The final sequence was a coronal gradient echo sequence with magnetization preparation and produced 128 coronal high - resolution T_1 - weighted images, which were used for structural image analysis (time of inversion [TI] = 600 msec, echo time = 3.4 msec, flip angle = 15^o, field of view = 22, slice thickness =1.7 mm, matrix = 256 x 192). Images were converted into NIFTI file format for further processing.

The functional imaging protocol. The functional imaging protocol consisted of axial gradient - echo planar images (EPI; repetition time/echo time = 2000/40 msec; matrix = 64 x 64; field of view = 24 cm) acquired continually during the experimental paradigm. Twenty-seven contiguous 5-mm slices were acquired within each repetition time. Each EPI acquisition was run for 404 volumes. The first four volumes were discarded. Visual stimuli were presented using a screen (IFIS, MRI Devices, Waukesha, Wisconsin) placed

in the bore of the magnet. The T1 sequence yielded 180 contiguous 1.2 - mm coronal slices (matrix = 192 x 192; field of view = 24 cm; flip angle = 8°).

5.2.5 Image processing and analysis

The EPI and T1 images were reconstructed into NIFTI format (Mayo Clinic, Rochester, Minnesota) using DICOM convert functions available in SPM5 (Statistical Parametric Mapping; The Wellcome Department of Imaging Neuroscience, The University College of London; http://www.fil.ion.ucl.ac.uk/spm/) running in Matlab version 7.1 (The Math Works, Natick, Massachusetts). EPI images were realigned to the mean functional image to correct for movement throughout the period of acquisition. The structural (source) and functional (reference) image were then coregistered, and the anatomic image was segmented. Spatial normalization parameters generated from the previous step were used to normalize at $2mm^3$ the realigned functional EPI data. Finally the realigned normalized images were smoothed with an 8x8x8 mm full width half maximum (FWHM) Gaussian filter.

5.2.6 Classification of orbitofrontal sulcogyral patterns

The protocol of sulcogyral patterns classification was developed based on that proposed by Chiavaras and Petrides (2000). This protocol was further enhanced in Chakirova and colleagues (2010). In greater details the protocol could be found in the **Appendix III** and **Chapters 1** and **3** of this thesis. See also **Figure 1.4** in **Chapter 1** of this thesis.

5.2.7 Identification of the cingulate and paracingulate sulci morphological variances

The rater was instructed to examine a mid - sagittal section, having located the anterior commissure and highlighted an area of the suspected paracingulate sulcus (PCS) in the transverse view. As per previous methods (Fornito *et al.,* 2008) the paracingulate sulcus was defined as a clearly identifiable sulcus running parallel and dorsal to the cingulate sulcus for > 20 mm. The cortex was rated over several slices to avoid including sulci that did not originate at the medial surface or that were in fact only superficial dimples. A paracingulate sulcus was classified as “present” if it was longer than 20 mm and “prominent” longer than 40 mm. If there was no apparent PCS, or it was < 20 mm, it was categorised as “absent.” Along the length of any PCS observed, an interruption of up to 10mm in length was allowed, as per (Fornito *et al.,* 2007), but any discontinuation greater than this was considered to be the end to that PCS. This resulted in the classification “interrupted”, and if there was no such segment of interruption, “continuous.”

5.2.8 Reliability of the OFC patterns classification protocol

The classification of the orbitofrontal sulcogyral patterns was carried out by G.C., blinded to subject group. Inter - rater reliability was assessed by two raters, who independently evaluated the sulcal patterns for 15 random cases (30 hemispheres: 15 in the right and 15 in the left), blinded to group membership. The intra - class correlation coefficients were 0.86 for right hemisphere and 0.84 for left hemisphere.

5.2.9 Reliability of the anterior cingulate morphology identification protocol

Two raters practiced the protocol until confident and then independently from each other rated the same twenty randomly chosen scans (forty hemispheres). Inter - rater reliability for the cingulate sulcus classification was 0.933 in the right hemisphere and 1.00 in the left hemisphere. Inter - rater reliability for the paracingulate sulcus classification was found to be 0.920 for the right hemisphere and 0.953 for the left hemisphere.

Intra - rater reliability was assessed in a subset of twenty scans (forty hemispheres). Intra - rater reliability for CS morphology was found to be 1.00 for the right hemisphere and 1.00 for the left hemisphere. Intra - rater reliability for denoting PCS morphology was found to be 0.899 for the right hemisphere and 0.952 for left hemisphere.

5.2.10 Statistical analysis

All statistical analyses were performed using the Statistical Program for the Social Sciences (SPSS, Chicago, Illinois) version 19 (http://www.spss.com/software).

Analysis of variance and chi-squared tests was applied to compare demographics between the groups. The distribution of the orbitofrontal sulcogyral patterns in the various groups was analysed using Kruskal - Wallis analysis. In order to facilitate comparison with previously published findings (Chiavaras and Petrides, 2000; Nakamura *et al.,* 2007), the orbitofrontal sulcogyral patterns were examined separately within right and left hemispheres. The contrasts of interests were: healthy controls versus patients with depression, healthy controls versus high risk individuals who

remained well, and high risk individuals who remained well versus those at high risk who became ill.

The gender effect on the distribution of the orbitofrontal and anterior cingulate morphology, the symmetry – asymmetry comparison of the orbitofrontal and anterior cingulate morphology between the groups, the distribution of the cingulate and paracingulate sulcul morphological variants between the groups and associations between orbitofrontal and anterior cingulate morphology were analysed using Kruskal - Wallis test.

Through **Chapters 3**, **4** and **5** of this thesis neuropsychological and structural association analyses of the orbitofrontal morphology were performed in a number of different cohorts. It was thought to examine whether there are some replicable features of the orbitofrontal patterns. These analyses included the examination of the relationships between the possession of particular orbitofrontal type and scores on the Hayling Sentence Completion Task, the IDED task and NEO-FFI questionnaire within the group of individuals at high genetic risk of developing bipolar disorder. In undertaking these analyses the right and left hemispheres were examined separately. To enable the examination of any such associations, participants were divided into those expressing type III in the right or left hemisphere and individuals without this orbitofrontal pattern in the right or left hemisphere accordingly (similar for types I and II). In these groups neuropsychological scores were compared using Kruskal - Wallis test. Further, the associations of the orbitofrontal sulcogyral patterns with the previously extracted volumes of different brain regions were also examined. The positive and negative predictive values as well as sensitivity and specificity were calculated.

5.3 Results

5.3.1 Demographics

There was no difference found between healthy volunteers, those individuals at high genetic risk of developing bipolar affective disorder that remained well and those of high risk individuals who developed depression either in age, handedness, gender, or IQ. Demographic details of both groups are listed in **Figure 5.1**.

Figure 5.1. Demographics of healthy controls and high - risk subgroups. High Risk well = those individuals from the high risk group who remained well. High Risk ill = those from the high risk group who developed depression.

	Healthy controls (n = 70)	High Risk well (n= 93)	High Risk ill (n = 28)	df	Pearson Chi-Square	P value
Gender (male:female)	31 : 39	46 : 47	12 : 16	2	0.614	0.735
Handedness (right:left:mixed)	63 : 5 : 0*	82 : 9 : 2	27 : 1 : 0	6	6.820	0.338
				df	**F**	**P value**
Age (mean +/- SD)	20.513 + / - 2.2094	21.122 + / - 2.8573	20.645 + / - 2.7024	2	1.430	0.489
NART (mean +/- SD)	108.69 + / - 7.385	108.70 + / - 9.325	108.07 + / - 6.532	2	0.593	0.743
FIQ	107.37 + / - 11.379	106.71 + / - 13.716	108.18 + / - 15.097	2	0.639	0.726
VIQ	106.89 + / - 13.330	105.13 + / - 15.741	108.65 + / - 15.582	2	0.964	0.617
The RISC total	25.94 + / - 9.321	29.28 + / - 9.295	37.90 + / - 6.385	2	12.205	0.002
The HRSD total	0.73 + / - 1.344	1.48 + / - 2.649	3.11 + / - 3.900	2	12.178	0.002
The YMRS total	0.21 + / - 0.789	0.27 + / - 0.700	0.50 + / - 1.072	2	3.066	0.216
Cylcothymia	2.58 + / - 3.106	2.74 + / - 2.663	4.87 + / - 3.757	2	8.892	0.012
Depressive	1.05 + / - 1.430	0.83 + / - 1.196	2.13 + / - 2.201	2	6.400	0.041
Anxiety	0.94 + / - 1.082	0.78 + / - 1.077	1.17 + / - 1.302	2	2.065	0.356
Neuroticism	20.55 + / - 8.635	21.49 + / - 9.124	30.83 + / - 10.671	2	15.885	0.000
Extravertism	31.14 + / - 5.549	29.64 + / - 5.515	25.17 + / - 7.152	2	12.334	0.002

Demographic variables are similar in all the main comparison groups (all p>0.05). *handedness data missing for 2 individuals.

5.3.2 Distribution of orbitofrontal patterns in healthy controls and the high risk groups

Type IV was present in either hemisphere in five healthy controls and in seven participants at high risk of developing bipolar affective disorder. Consistent with the analyses in the previous chapters of this thesis the orbitofrontal type IV was excluded from further statistical examination as its numbers were relatively small.

Figure 5.2. Distribution of the orbitofrontal patterns (Type I, II and III) in the Bipolar Family Study. Comparison with findings of Nakamura and colleagues (2007) and Chiavaras and Petrides (2000). HC = Healthy Controls. Sch = Patients with schizophrenia.

	Type I (n, %)	Type II (n, %)	Type III (n, %)
Right Hemisphere			
Healthy Controls	41 (62.1 %)	18 (27.3 %)	7 (10.6 %)
High Risk well	55 (63.9 %)	23 (26.80 %)	8 (9.3 %)
High Risk ill	10 (41.7%)	5 (20.8 %)	9 (37.5 %)
Chiavaras, HC	64 %	26 %	10 %
Nakamura, HC	62 %	28 %	10 %
Nakamura, Sch	42 %	34 %	24 %
Left Hemisphere			
Healthy Controls	33 (52.4 %)	18 (28.6 %)	12 (19.1 %)
High Risk well	44 (54.3 %)	24 (29.6 %)	13 (16.1 %)
High Risk ill	8 (33.3 %)	7 (29.2 %)	9 (37.5 %)
Chiavaras, HC	48 %	34 %	18 %
Nakamura, HC	46 %	36 %	18 %
Nakamura, Sch	40 %	34 %	26 %

At the time of second assessment it appears that twenty four participants at high risk of developing bipolar disorder and four healthy controls were showing symptoms of depression. So, the controls that became ill were removed from the further analysis and twenty four participants from the high risk who developed depression were separated into the third group of those at high risk who became ill. With both genders included there was a significant difference found in distribution of the orbitofrontal patterns in the right hemisphere between the groups (Kruskal - Wallis = 6.628, df = 2, p =

0.036), but not in the left hemisphere (Kruskal - Wallis = 2.398, df = 2, p = 0.302). This difference was arising from the distribution of the orbitofrontal type III in the right hemisphere (Kruskal - Wallis = 13.015, df = 2, p = 0.001; See **Figure 5.2**). There was also a trend found in the distribution of the orbitofrontal type III in the left hemisphere (Kruskal - Wallis = 5.863, df = 2, p = 0.053). With both genders included there was no difference found between healthy volunteers and those of the high risk group who remain well either in the right hemisphere (Kruskal Wallis = 0.198, df = 1, p = 0.657) or in the left hemisphere (Kruskal Wallis = 0.105, df = 1, p = 0.746). However, there was a difference found in distribution of the orbitofrontal patterns between healthy controls and those at high risk who developed depression in the right hemisphere (Kruskal Wallis = 4.608, df = 1, p = 0.032) arising from the increased frequency of the orbitofrontal type III in the right hemisphere in the ill high risk group (Kruskal Wallis = 8.826, df = 1, p = 0.003). There was also observed an increased frequency of the type III in the left hemisphere in those at high risk who became ill when compared to healthy controls (Kruskal Wallis = 3.778, df = 1, p = 0.052). There was a significant difference found between both high risk groups (those who remained well and those who became ill) in distribution of the orbitofrontal patterns in the right hemisphere (Kruskal Wallis = 6.655, df = 1, p = 0.010) deriving from the reduced frequency of type I (Kruskal Wallis = 3.820, df = 1, p = 0.051) and an increased frequency of type III (Kruskal Wallis = 11.314, df = 1, p = 0.001) in those who became ill. These two groups also differed in the distribution of type III in the left hemisphere (Kruskal Wallis = 5.822, df = 1, p = 0.016) that was present more frequently in those high risk that became ill.

5.3.3 Gender effect on the distribution of the orbitofrontal morphology

There was not any convincing gender effect found in distribution of the orbitofrontal patterns when healthy controls were compared to those at high risk of developing bipolar disorder who remained well (See **Figure 5.3**).

There was a significant difference found in the distribution of the orbitofrontal patterns in the right hemisphere in males (Kruskal - Wallis = 11.802, df = 1, p = 0.001), but not in females (Kruskal - Wallis = 0.003, df = 1, p = 0.955) when healthy controls were compared to those males at high risk that became ill. This difference was arriving from the reduction of type I (Kruskal - Wallis = 9.333, df = 1, p = 0.002) and an increased frequency of type III (Kruskal - Wallis = 9.108, df = 1, p = 0.003) in the right hemisphere in those males at high risk who became ill.

Direct comparison revealed a significant difference in distribution of the orbitofrontal patterns in the right hemisphere in males (Kruskal - Wallis = 8.101, df = 1, p = 0.004), but not in females (Kruskal - Wallis = 1.638, df = 1, p = 0.201) when the high risk participants who remained well were compared to those individuals at high risk who developed depression. This difference was arriving from the reduction of type I (Kruskal - Wallis = 5.550, df = 1, p = 0.018) and an increased frequency of type III (Kruskal - Wallis = 7.149, df = 1, p = 0.007) in the right hemisphere in those at high risk who became ill.

Moreover, there was a difference found in distribution of the orbitofrontal patterns in the left hemisphere in females (Kruskal - Wallis = 3.567, df = 1, p = 0.059), when the high risk participants who remained well were compared to those at high risk who developed depression. This difference was arriving from the reduction of type I (Kruskal - Wallis = 2.979, df = 1, p = 0.084) and an increased frequency of type III (Kruskal - Wallis = 3.181, df = 1, p = 0.075) in the left hemisphere in those female participants from the high risk group who became ill. Furthermore, the female individuals who became ill also had a prevalence of type III in the right hemisphere (Kruskal - Wallis = 4.445, df = 1, p = 0.035) when compared to the female at high risk that remained well.

Figure 5.3. Distribution of the orbitofrontal patterns in diagnostic groups by gender (in numbers).

	Type I	Type II	Type III	Type IV
Right hemisphere				
Healthy controls (m : f)	19 : 20	7 : 10	1 : 6	0 : 1
High Risk well (m : f)	24 : 30	16 : 7	4 : 4	0 : 0
High Risk ill (m : f)	1 : 9	4 : 1	4 : 5	0 : 0
Left hemisphere				
Healthy controls (m : f)	14 : 17	8 : 9	4 : 8	1 : 3
High Risk well (m : f)	16 : 27	17 : 7	6 : 7	5 : 0
High Risk ill (m : f)	2 : 6	4 : 3	3 : 6	0 : 0

5.3.4 The symmetry - asymmetry comparison of orbitofrontal morphology between the groups

As previously scans were considered symmetric if they contained the same orbitofrontal pattern in the right and in the left hemisphere: type I in the right and type I in the left hemispheres, type II in the right and type II in the left hemispheres, or type III in the right and type III in the left hemispheres. Scans were named asymmetric if they contained different orbitofrontal sulcogyral patterns in the right and in the left hemispheres (any other non - symmetric combination).

There was no difference found in distribution of symmetric and asymmetric scans with both males and females included (Kruskal - Wallis = 0.172, df = 1, p = 0.679), or either in males (Kruskal - Wallis = 0.154, df = 1, p = 0.694) or in females (Kruskal -Wallis = 0.037, df = 1, p = 0.847) separately when healthy controls and all individuals at high risk of developing bipolar affective

disorder were compared. When the high risk group was subdivided into those who remained well and those who became ill, there was no difference found in distribution of symmetric and asymmetric scans either between any of the groups.

5.3.5 Distribution of the cingulate and paracingulate sulcus morphological variants between the main groups

Anterior cingulate morphology

Given that the cingulate sulcus is always present the morphological variants of the cingulate sulcus were examined. An accepted classification of the anterior cingulate morphology is based on the continuity of the CS, that is whether it has a single continuous form or is fragmented into pieces. The number of CS pieces was compared between the groups. With both males and females combined there was no difference found in distribution of the cingulate morphology between healthy controls, those at high risk of developing bipolar disorder who remained well and those at high risk who became ill (Kruskal - Wallis = 1.401, df = 2, p = 0.496 in the right hemisphere and Kruskal -Wallis = 0.023, df = 2, p = 0.988 in the left hemisphere).

Paracingulate morphology

With both males and females included there was a significant difference found in the distribution of the paracingulate sulcus variants in the left hemisphere (Kruskal - Wallis = 6.910, df = 1, p = 0.009) when healthy controls and those at high risk of developing bipolar disorder who remained well were compared in such a way that there was a reduction of the absent PCS variant and an increased frequency of the prominent PCS variant found in the high risk group.

When those at high risk of developing bipolar disorder who remained well were compared to those at high risk who became ill there was an increased frequency of the absent PCS variant (Kruskal - Wallis = 9.917, df = 1, p = 0.002) and a decreased frequency of the PCS present and prominent variants (Kruskal - Wallis = 6.078, df = 1, p = 0.014) observed in those at high risk who became ill in the left hemisphere.

The comparison of those at high risk of developing bipolar disorder who became ill to healthy individuals revealed a reduced frequency of the present PCS variant in the left hemisphere in the high risk group (Kruskal - Wallis = 2.915, df = 1, p = 0.088).

5.3.6 Gender effect on the distribution of the cingulate and paracingulate sulcus morphological variants between the main groups

Given that a gender effect was discovered on the orbitofrontal morphology it was important to examine whether the anterior cingulate morphology would have this effect and if so, whether this effect would be similar to the one found for the orbitofrontal morphology. Direct comparison did not reveal any difference in distribution of the cingulate morphology between healthy controls, those at high risk of developing bipolar disorder who remained well and those at high risk who became ill either in males, or in females.

There was a significant difference found in distribution of the PCS variants in the left hemisphere in female participants when all three groups were compared (Kruskal -Wallis = 6.985, df = 1, p = 0.030).

Despite absence of any between group differences of the paracingulate morphology in the right hemisphere it was considered to be important to examine whether there is any gender effect on the distribution of the paracingulate sulcus between the groups in both right and left hemispheres.

The direct group comparison revealed that female control participants had an increased frequency of the prominent PCS in the right hemisphere compared to both high - risk participants who remained well (Kruskal -Wallis = 3.620, df = 1, p = 0.057) and those at high risk who became ill (Kruskal -Wallis = 7.136, df = 1, p = 0.008).

Moreover, there was a significant difference found in distribution of the PCS variants in the left hemisphere in female participants with its reduced frequency of the absent PCS (Kruskal - Wallis = 6.324, df = 1, p = 0.012) and an increased frequency of the prominent PCS variant in those at high risk who remained well compared to healthy individuals (Kruskal - Wallis = 4.261, df = 1, p = 0.039).

There was also difference found in the distribution of the PCS in the left (Kruskal -Wallis = 5.128, df = 1, p = 0.024) and right hemisphere (Kruskal - Wallis = 3.053, df = 1, p = 0.081) when female participants of those at high - risk who remained well had an increased frequency of the prominent PCS variant in the right hemisphere (Kruskal - Wallis = 5.283, df = 1, p = 0.022) and were more likely to have the connected PCS (a single piece) in the left hemisphere (Kruskal - Wallis = 8.397, df = 1, p = 0.004) compared to those high risk who became ill. However, there was no gender effect found on expression of the prominent PCS either in female (Kruskal - Wallis = 2.917, df = 2, p = 0.233) or male (Kruskal - Wallis = 1.254, df = 2, p = 0.534) participants in the left hemisphere.

5.3.7 Symmetry - asymmetry of the cingulate variants between the groups

For this type of comparison scans were rated as symmetric if they had the same variant of the cingulate sulcus (a single piece only or ‘broken’ into segments only) in the right and in the left hemispheres. All the other scans

were rated as asymmetric. In order to examine the PCS symmetry scans were rated as symmetric if they possessed the same variant of the paracingulate sulcus (absent, present or prominent) in the right and in the left hemisphere. All the other scans were rated as asymmetric. There was no difference found in the CS or PCS symmetry - asymmetry score between the groups with both genders included or separately either in males or in females.

5.3.8 Associations between orbitofrontal and anterior cingulate morphology

In order to be able to compare findings in the BFS with similar ones in the EHRS the associations were examined between the orbitofrontal and anterior cingulate morphology separately in healthy volunteers and in those individuals at high genetic risk of developing bipolar affective disorder as it was done in **Chapter 4**. A gender effect on this association was also investigated.

Healthy controls

With both genders combined there was an association found between the orbitofrontal morphology in the right hemisphere and the paracingulate sulcus in the right hemisphere (Kruskal - Wallis = 4.460, df = 1, p = 0.035) in such a way that those with the orbitofrontal type I (Kruskal - Wallis = 3.916, df = 1, p = 0.048) in the right hemisphere were less likely to have the absent paracingulate sulcus in the right hemisphere.

Healthy individuals with the orbitofrontal type II in the left hemisphere were less likely to have the PCS in the right hemisphere present (Kruskal - Wallis = 4.729, df = 1, p = 0.030).

Also individuals with the orbitofrontal type III in the left hemisphere were more likely to have the PCS in the right hemisphere absent (Kruskal - Wallis = 4.107, df = 1, p = 0.043) and less likely to have the PCS in the right hemisphere prominent (Kruskal -Wallis = 4.371, df = 1, p = 0.043). There was no association found between the orbitofrontal morphology and the cingulate sulcus in the right or left hemispheres.

Individuals at high risk of developing bipolar disorder who remained well

There was an association found between the orbitofrontal patterns and paracingulate morphology in the left hemisphere in such a way that participants with the orbitofrontal type I in the left hemisphere were more likely to have the PCS in the left hemisphere absent (Kruskal - Wallis = 4.225, df = 1, p = 0.040).

There was an association found between the orbitofrontal patterns and paracingulate morphology in the right hemisphere in such a way that participants with the orbitofrontal type III in the right hemisphere were more likely to have the PCS in the right hemisphere absent (Kruskal - Wallis = 3.418, df = 1, p = 0.064).

There was an association found between the orbitofrontal patterns in the right hemisphere and the paracingulate morphology in the left hemisphere in such a way that participants with the orbitofrontal type II (Kruskal - Wallis = 6.782, df = 1, p = 0.009) and without the orbitofrontal type I (Kruskal - Wallis = 3.742, df = 1, p = 0.053) in the right hemisphere were more likely to have the prominent PCS variant in the left hemisphere.

Individuals at high risk of developing bipolar disorder who became ill

There was an association found between the orbitofrontal patterns in the left hemisphere and the present PCS in the right hemisphere (Kruskal - Wallis = 4.349, df = 1, p = 0.037) in such a way that participants with the orbitofrontal type III in the left hemisphere were more likely to have the present PCS variant in the right hemisphere (Kruskal - Wallis = 5.476, df = 1, p = 0.019).

5.3.9 Association between cingulate and paracingulate sulci

Healthy controls

With both genders combined there was an association found between the right cingulate sulcus and the right (Kruskal - Wallis = 4.110, df = 1, p = 0.043) and left paracingulate sulci in healthy controls in such a way that healthy individuals with the present PCS variant in the left hemisphere (Kruskal - Wallis = 3.441, df = 1, p = 0.064) and with the present or prominent PCS in the right hemisphere (Kruskal - Wallis = 4.213, df = 1, p = 0.040) will be less likely to have the connected cingulate sulcus in the right hemisphere.

Individuals at high risk of developing bipolar disorder who remained well

There were not any associations found between the cingulate and paracingulate morphological variants in this group with both males and females combined.

Individuals at high risk of developing bipolar disorder who became ill

With both genders combined there was an association found between the right cingulate sulcus and the right paracingulate morphology in such a way

that individuals with the present PCS variant in the left hemisphere (Kruskal - Wallis = 3.800, df = 1, p = 0.051) were less likely to have the connected cingulate sulcus in the right hemisphere.

5.3.10 Neuropsychological and clinical associations of orbitofrontal morphology

For consistency with **Chapter 4** neuropsychological and clinical associations of the orbitofrontal pattern morphological variants were examined in the high risk participants of developing bipolar affective disorder as the participants of this group were scanned when they were well. Positive and negative predictive values of the orbitofrontal and anterior cingulate morphology were also investigated as it was considered important to examine whether orbitofrontal morphology on its own or in combination with the anterior cingulate morphological variants might improve the prediction of bipolar disorder in the high risk individuals. Neuropsychological and clinical associations of orbitofrontal sulcogyral patterns in healthy individuals were not analysed as an intention was to compare such associations between two large high risk groups (of developing schizophrenia – **Chapter 4** and of developing bipolar disorder – **Chapter 5**) in **Chapter 8** and because the volume of this thesis is limited.

5.3.10.1 The IQ scores and the orbitofrontal morphology

Considering that the orbitofrontal patterns were previously found to be associated with intelligence (Nakamura *et al.,* 2007), it was important to examine whether the presence of the orbitofrontal morphological variants in the high - risk participants were associated with the WASI or / and the NART scores.

There was an association found between the orbitofrontal type III in the right hemisphere and the verbal IQ (Kruskal - Wallis = 3.463, df = 1, p = 0.063) in male participants in such a way that those male participants with the orbitofrontal type III in the right hemisphere scored less than those with any other type.

With both males and females combined there was an association found between the orbitofrontal type II in the left hemisphere and the WASI full scale IQ (Kruskal - Wallis = 3.127, df = 1, p = 0.077) in high risk participants in such a way that those individuals with the orbitofrontal type II in the left hemisphere scored higher than those with any other type in the left hemisphere. It became evident that this difference was more explicit in male participants (Kruskal - Wallis = 3.871, df = 1, p = 0.049), but not in females (Kruskal - Wallis = 0.003, df = 1, p = 0.959).

There was an association found between the orbitofrontal type III in the left hemisphere and the WASI verbal IQ (Kruskal - Wallis = 3.830, df = 1, p = 0.050) and full scale IQ (Kruskal - Wallis = 3.656, df = 1, p = 0.056) in such a way that those participants with the orbitofrontal type III in the left hemisphere scored less than those with any other type. This difference was more evident in male participants (Kruskal - Wallis = 3.296, df = 1, p = 0.069 for full scale IQ and Kruskal - Wallis = 3.589, df = 1, p = 0.058 for verbal IQ).

5.3.10.2 The IDED test and orbitofrontal morphology

The associations between the orbitofrontal sulcogyral patterns and the performance during the IDED test were examined in participants at high genetic risk of developing bipolar disorder. A number of such associations was identified in this study. Importantly, at least some of those associations were affected by gender.

There was an association found between the orbitofrontal type I in the right hemisphere and a number of trials (Kruskal - Wallis = 4.396, df = 1, p = 0.036) and errors (Kruskal - Wallis = 3.726, df = 1, p = 0.054) during intra - dimensional set -shifting stage in such a way that the high risk participants of developing bipolar disorder with the orbitofrontal type I in the right hemisphere required more trial to complete intra - dimensional set - shifting stage and made more errors than individuals with any other type in the right hemisphere. These associations were more evident in male participants (Kruskal - Wallis = 3.943, df = 1, p = 0.047 for the number of trials, Kruskal - Wallis = 2.999, df = 1, p = 0.083 for the number of errors during the intra - dimensional stage). This means that participants with type I in the right hemisphere experienced some difficulties at the beginning of the task.

There was an association found between the orbitofrontal type II in the right hemisphere and a number of trials (Kruskal - Wallis = 3.978, df = 1, p = 0.046) and errors (Kruskal - Wallis = 3.222, df = 1, p = 0.073) during intra - dimensional set - shifting stage in such a way that the male high risk participants of developing bipolar disorder with the orbitofrontal type II in the right hemisphere required less intra – dimensional trials to complete intra - dimensional set - shifting stage and made less errors than male individuals with any other type in the right hemisphere. This means that they performed better than male participants without type II in the right hemisphere.

There was an association found between the orbitofrontal type III in the right hemisphere and a number of trials (Kruskal - Wallis = 13.110, df = 1, p < 0.0001) and errors (Kruskal - Wallis = 12.367, df = 1, p < 0.0001) during intra - dimensional reversal set - shifting stage in such a way that the high - risk participants of developing bipolar disorder with the orbitofrontal type III in the right hemisphere required to complete more intra - dimensional reversal trials and made more errors than individuals with any other type in the right hemisphere. This means that they experienced difficulties during the reversal

stage and their difficulties were greater than those of the participants with the orbitofrontal type I as the reversal stage is considered to be more difficult than the intra - dimensional set - shifting stage. Further, these differences originated in both males (Kruskal - Wallis = 6.160, df = 1, p = 0.013 for the number of trials and Kruskal - Wallis = 5.529, df = 1, p = 0.019 for the number for errors) and females (Kruskal - Wallis = 8.000, df = 1, p = 0.005 for the number of trials and Kruskal - Wallis = 8.000, df = 1, p = 0.005 for the number of errors).

There was an association found between the orbitofrontal type I in the left hemisphere and a total reaction time (Kruskal - Wallis = 7.766, df = 1, p = 0.005) during the IDED task performance in such a way that the high risk participants of developing bipolar disorder with the orbitofrontal type I in the left hemisphere had greater reaction time compared to participants with any other type in the left hemisphere. This difference originated in females with the orbitofrontal type I in the left hemisphere who had greater reaction time (Kruskal - Wallis = 6.136, df = 1, p = 0.013), made less errors overall (Kruskal - Wallis = 3.309, df = 1, p = 0.069) and especially during extra - dimensional set - shifting stage (Kruskal - Wallis = 4.061, df = 1, p = 0.044), and required less trials to complete extra - dimensional stage (Kruskal - Wallis = 4.506, df = 1, p = 0.034). This means that they performed better than participants without type I in the left hemisphere.

There was an association found between the orbitofrontal type II in the left hemisphere and a number of trials (Kruskal - Wallis = 4.149, df = 1, p = 0.042), errors (Kruskal - Wallis = 3.594, df = 1, p = 0.058) and a reaction time (Kruskal - Wallis = 3.379, df = 1, p = 0.066) during extra - dimensional reversal stage in such a way that the high risk participants of developing bipolar disorder with the orbitofrontal type II in the left hemisphere required more trial to complete extra - dimensional reversal stage and made more errors than individuals with any other type in the left hemisphere.

There was an association found between the orbitofrontal type III in the left hemisphere and a total reaction time (Kruskal - Wallis = 4.983, df = 1, p = 0.026) during the IDED task performance especially during intra - dimensional set - shifting trial (Kruskal - Wallis = 5.984, df = 1, p = 0.014). This difference originated in females (Kruskal - Wallis = 6.752, df = 1, p = 0.009 for the total reaction time and Kruskal - Wallis = 4.238, df = 1, p = 0.040 for the reaction time during the intra -dimensional set-shifting stage).

5.3.10.3 The HSCT test and orbitofrontal morphology

The orbitofrontal type I in the right hemisphere

With both males and females included there was an association found between the orbitofrontal type I in the right hemisphere and a word appropriateness scores for the medium low constraint sentences (Kruskal - Wallis = 3.589, df = 1, p = 0.058) in such a way that the high risk participants of developing bipolar disorder with the orbitofrontal type I in the right hemisphere scored more than individuals with any other type in the right hemisphere.

The orbitofrontal type II in the right hemisphere

With both males and females included there was an association found between the orbitofrontal type II in the right hemisphere and a performance during medium low constraint (Kruskal - Wallis = 3.689, df = 1, p = 0.055) in such a way that the high - risk participants of developing bipolar disorder with the orbitofrontal type II in the right hemisphere scored less than individuals with any other type in the right hemisphere.

There was a gender effect found in the association between the orbitofrontal type II in the right hemisphere and a performance during medium high

constraint (Kruskal - Wallis = 3.636, df = 1, p = 0.057) in such a way that the male high risk participants of developing bipolar disorder with the orbitofrontal type II in the right hemisphere scored less than male individuals with any other type in the right hemisphere.

The orbitofrontal type III in the right hemisphere

There was a gender effect found in the association between the orbitofrontal type III in the right hemisphere and a performance during medium high constraint (Kruskal - Wallis = 2.905, df = 1, p = 0.088) in such a way that the male high risk participants of developing bipolar disorder with the orbitofrontal type III in the right hemisphere scored more than male individuals with any other type in the right hemisphere.

The orbitofrontal type III in the left hemisphere

With both males and females included there was an association found between the orbitofrontal type III in the left hemisphere and a performance during low constraint (Kruskal - Wallis = 5.517, df = 1, p = 0.019) in such a way that the high - risk participants of developing bipolar disorder with the orbitofrontal type III in the left hemisphere scored less than individuals with any other type in the left hemisphere.

There was a gender effect found in the association between the orbitofrontal type III in the left hemisphere and a performance during medium high constraint (Kruskal - Wallis = 3.630, df = 1, p = 0.057) in such a way that the female high risk participants of developing bipolar disorder with the orbitofrontal type III in the left hemisphere scored more than female individuals with any other type in the left hemisphere.

There was a gender effect found in the association between the orbitofrontal type III in the left hemisphere and a performance during low constraint (Kruskal - Wallis = 4.714, df = 1, p = 0.030), during medium high constraint (Kruskal - Wallis = 3.276, df = 1, p = 0.070) and high constraint (Kruskal - Wallis = 4.074, df = 1, p = 0.044) in such a way that the male high risk participants of developing bipolar disorder with the orbitofrontal type III in the left hemisphere scored less during low constraint, medium high constraint and high constraint than male individuals with any other type in the left hemisphere.

5.3.10.4 The personality and temperamental traits and orbitofrontal morphology

The orbitofrontal type I in the right hemisphere

With both males and females included there was an association found between the orbitofrontal type I in the right hemisphere and irritability (Kruskal - Wallis = 3.949, df = 1, p = 0.047) in such a way that the high risk participants of developing bipolar disorder with the orbitofrontal type I in the right hemisphere scored more than individuals with any other type in the right hemisphere.

The orbitofrontal type II in the right hemisphere

There was a gender effect found in the association between the orbitofrontal type II in the right hemisphere and cyclothymia (Kruskal - Wallis = 4.229, df = 1, p = 0.040) and depression (Kruskal - Wallis = 5.074, df = 1, p = 0.024) in such a way that the female high risk participants of developing bipolar disorder with the orbitofrontal type II in the right hemisphere scored less in cyclothymia and depression than female individuals with any other type in the right hemisphere.

The orbitofrontal type III in the right hemisphere

There was a gender effect found in the association between the orbitofrontal type III in the right hemisphere and sadness (Kruskal - Wallis = 5.425, df = 1, p = 0.020) and openness (Kruskal - Wallis = 3.489, df = 1, p = 0.062) in such a way that the male high risk participants of developing bipolar disorder with the orbitofrontal type III in the right hemisphere scored less in openness and were less able to identify sadness as a face expression than male individuals with any other type in the right hemisphere.

The orbitofrontal type I in the left hemisphere

There was a gender effect found in the association between the orbitofrontal type I in the left hemisphere and openness (Kruskal - Wallis = 3.830, df = 1, p = 0.050), agreeableness (Kruskal - Wallis = 7.874, df = 1, p = 0.005), irritability (Kruskal - Wallis = 3.954, df = 1, p = 0.047), and hyperthymia (Kruskal - Wallis = 4.765, df = 1, p = 0.029) in such a way that the female high risk participants of developing bipolar disorder with the orbitofrontal type I in the left hemisphere scored more in openness, hyperthymia and irritability, and less in agreeableness than female individuals with any other type in the left hemisphere.

The orbitofrontal type II in the left hemisphere

There was a gender effect found in the association between the orbitofrontal type II in the left hemisphere and agreeableness (Kruskal - Wallis = 5.746, df = 1, p = 0.017), hyperthymia (Kruskal - Wallis = 7.800, df = 1, p = 0.005) and irritability (Kruskal - Wallis = 9.476, df = 1, p = 0.002) in such a way that the female high risk participants of developing bipolar disorder with the orbitofrontal type II in the left hemisphere scored less in irritability and

hyperthymia, and more in agreeableness than female individuals with any other type in the left hemisphere.

The orbitofrontal type III in the left hemisphere

With both males and females included there was an association between the orbitofrontal type III in the left hemisphere and openness (Kruskal - Wallis = 7.568, df = 1, p = 0.006), conscientiousness (Kruskal - Wallis = 3.713, df = 1, p = 0.054) and neuroticism (Kruskal - Wallis = 3.364, df = 1, p = 0.067) in such a way that the high risk participants of developing bipolar disorder with the orbitofrontal type III in the left hemisphere scored more in conscientiousness, less in openness, and more in neuroticism than individuals with any other type in the left hemisphere.

There was a gender effect found in the association between the orbitofrontal type III in the left hemisphere and conscientiousness (Kruskal - Wallis = 3.567, df = 1, p = 0.059) in such a way that the female high risk participants of developing bipolar disorder with the orbitofrontal type III in the left hemisphere scored more in conscientiousness than female individuals with any other type in the left hemisphere.

There was a gender effect found in the association between the orbitofrontal type III in the left hemisphere and openness (Kruskal - Wallis = 4.829, df = 1, p = 0.028) in such a way that the male high risk participants of developing bipolar disorder with the orbitofrontal type III in the left hemisphere scored less in openness than male individuals with any other type in the left hemisphere.

5.3.10.5 The HRSD and orbitofrontal morphology

The orbitofrontal type III in the right hemisphere

There was an association found between the orbitofrontal type III in the right hemisphere and the HRSD scores (Kruskal - Wallis = 2.886, df = 1, p = 0.089) in such a way that the female participants at high risk of developing bipolar disorder with the orbitofrontal type III in the right hemisphere scored more than the female individuals with any other type in the right hemisphere.

5.3.10.6 The YMRS and orbitofrontal morphology

The orbitofrontal type I in the left hemisphere

With both males and females included there was an association found between the orbitofrontal type I in the left hemisphere and the YMRS score (Kruskal - Wallis = 4.952, df = 1, p = 0.026) in such a way that the high risk participants of developing bipolar disorder with the orbitofrontal type I in the left hemisphere scored more than individuals with any other type in the left hemisphere. This association was driven by male participants score (Kruskal - Wallis = 3.441, df = 1, p = 0.064).

5.3.10.7 The RISC and orbitofrontal morphology

The orbitofrontal type II in the right hemisphere

There was an association found between the orbitofrontal type II in the right hemisphere and the RISC score (Kruskal - Wallis = 4.105, df = 1, p = 0.043) in such a way that the high risk participants of developing bipolar disorder with the orbitofrontal type II in the right hemisphere scored less than individuals with any other type in the right hemisphere.

5.3.10.8 The brain volume and the orbitofrontal morphology

In **Chapter 6** it will be examined whether there are associations between orbitofrontal morphology and grey and white matter density using Voxel-Based Morphology technique in healthy controls. In this chapter it was investigated whether there is any association between the volume of different brain parts and orbitofrontal morphology. These volumes were obtained by performing the brain parcellation technique in the FreeSurver software (http://surfer.nmr.mgh.harvard.edu/). As different participants were used in **Chapter 6** compared to the participants in this chapter, it might be important to know whether the same associations could be replicated in various studies with different participants.

The orbitofrontal type I in the right hemisphere

With both males and females combined there was an association found between the orbitofrontal type I in the right hemisphere and the volume of the left middle temporal lobe (Kruskal - Wallis = 7.653, df = 1, p = 0.006), in such a way that participants at high risk without orbitofrontal type I in the right hemisphere had larger volume of the left middle temporal lobe than those with the orbitofrontal type I in the right hemisphere.

There was a gender effect found on the association between the orbitofrontal type I in the right hemisphere and the volume of the right superior frontal gyrus (Kruskal - Wallis = 3.222, df = 1, p = 0.073) in such a way that female participants at high risk with the orbitofrontal type I in the right hemisphere had smaller volume of the right superior frontal gyrus compared to those female individuals at high risk with any other orbitofrontal pattern in the right hemisphere.

There was a gender effect found on the association between the orbitofrontal type I in the right hemisphere and the volume of the left middle temporal gyrus (Kruskal - Wallis = 4.062, df = 1, p = 0.044), the isthmus of the cingulate gyrus in the right hemisphere (Kruskal - Wallis = 3.209, df = 1, p = 0.073) and the left medial orbitofrontal gyrus (Kruskal - Wallis = 3.209, df = 1, p = 0.073) in such a way that male participants at high risk with the orbitofrontal type I in the right hemisphere had smaller volume of the left middle temporal gyrus, larger volume of the isthmus of the cingulate gyrus in the right hemisphere and smaller volume of the left medial orbitofrontal gyrus compared to those male individuals at high risk with any other orbitofrontal pattern in the right hemisphere.

The orbitofrontal type II in the right hemisphere

With both males and females included there was a significant association found between the orbitofrontal type II in the right hemisphere and the volume of the left middle temporal lobe (Kruskal - Wallis = 7.187, df = 1, p = 0.007), in such a way that participants at high risk without orbitofrontal type II in the right hemisphere had a smaller volume of the left middle temporal lobe compared to those at high risk with the orbitofrontal type II in the right hemisphere.

There was a gender effect found on the association between the orbitofrontal type II in the right hemisphere and the volume of the left middle temporal lobe (Kruskal - Wallis = 3.349, df = 1, p = 0.067) and left medial orbitofrontal cortex (Kruskal - Wallis = 3.001, df = 1, p = 0.083) in such a way that male participants at high risk with the orbitofrontal type II in the right hemisphere had larger volume of the left middle temporal lobe and left medial orbitofrontal cortex compared to those male individuals at high risk with any other orbitofrontal pattern in the right hemisphere.

The orbitofrontal type III in the right hemisphere

With both males and females combined there was an association found between the orbitofrontal type III in the right hemisphere and the volume of the isthmus of the cingulate gyrus in the left hemisphere (Kruskal - Wallis = 3.317, df = 1, p = 0.069) in such a way that participants at high risk with the orbitofrontal type III in the right hemisphere had a larger volume of the isthmus of the cingulate gyrus in the left hemisphere compared to those at high risk with any other orbitofrontal pattern in the right hemisphere.

There was a gender effect found on the association between the orbitofrontal type III in the right hemisphere and the volume of the isthmus of the cingulate gyrus in the right hemisphere (Kruskal - Wallis = 6.384, df = 1, p = 0.012), and right posterior cingulate cortex (Kruskal - Wallis = 3.653, df = 1, p = 0.056) in such a way that female participants at high risk with the orbitofrontal type III in the right hemisphere had larger volume of the isthmus of the cingulate gyrus in the right hemisphere and the right posterior cingulate cortex compared to those female individuals at high risk with any other orbitofrontal pattern in the right hemisphere.

The orbitofrontal type I in the left hemisphere

With both males and females included there was a significant association found between the orbitofrontal type I in the left hemisphere and the volume of the right rostral middle frontal lobe (Kruskal - Wallis = 4.695, df = 1, p = 0.030), left posterior cingulate cortex (Kruskal - Wallis = 3.522, df = 1, p = 0.061), and left frontal pole (Kruskal - Wallis = 3.247, df = 1, p = 0.072) in such a way that participants at high risk with orbitofrontal type I in the left hemisphere had larger volume of the right rostral middle frontal cortex, larger left posterior cingulate and larger left frontal pole compared to those at high risk with any other orbitofrontal pattern in the hemisphere.

There was a gender effect found on the association between the orbitofrontal type I in the left hemisphere and the volume of right rostral middle frontal cortex (Kruskal - Wallis = 5.988, df = 1, p = 0.014), left posterior cingulate cortex (Kruskal - Wallis = 10.525, df = 1, p = 0.001), right caudal anterior cingulate cortex (Kruskal - Wallis = 4.778, df = 1, p = 0.029), and left frontal pole (Kruskal - Wallis = 3.393, df = 1, p = 0.065) in such a way that female participants at high risk with the orbitofrontal type I in the left hemisphere had larger volume of the left frontal pole, right caudal anterior cingulate cortex, right rostral middle frontal cortex and left posterior cingulate cortex compared to those female individuals at high risk with any other orbitofrontal pattern in the left hemisphere.

The orbitofrontal type II in the left hemisphere

With both males and females included there was an association found between the orbitofrontal type II in the left hemisphere and the volume of the right rostral middle frontal cortex (Kruskal - Wallis = 3.606, df = 1, p = 0.058) and left rostral middle frontal cortex (Kruskal - Wallis = 3.054, df = 1, p = 0.081) in such a way that participants at high risk with the orbitofrontal type II in the left hemisphere had smaller volume of the right and left rostral middle frontal cortex compared to those at high risk with any other orbitofrontal pattern in the left hemisphere.

There was a gender effect on found the association between the orbitofrontal type II in the left hemisphere and the volume of right rostral middle frontal cortex (Kruskal - Wallis = 4.918, df = 1, p = 0.027) and left posterior cingulate cortex (Kruskal - Wallis = 3.631, df = 1, p = 0.057) in such a way that female participants at high risk with the orbitofrontal type II in the left hemisphere had smaller volume of the right rostral middle frontal cortex and left posterior cingulate cortex compared to those female individuals at high risk with any other orbitofrontal pattern in the left hemisphere.

The orbitofrontal type III in the left hemisphere

With both males and females included there was a significant association found between the orbitofrontal type III in the left hemisphere and the volume of the left posterior cingulate cortex (Kruskal - Wallis = 7.514, df = 1, p = 0.006) and left frontal pole (Kruskal - Wallis = 3.675, df = 1, p = 0.055) in such a way that participants at high risk with the orbitofrontal type III in the left hemisphere had smaller volume of the left posterior cingulate cortex and left frontal pole compared to those at high risk with any other orbitofrontal pattern in the left hemisphere.

The difference in the left posterior cingulate cortex originated in females (Kruskal - Wallis = 4.765, df = 1, p = 0.029) while the difference in the left frontal pole originated in males (Kruskal - Wallis = 3.538, df = 1, p = 0.060).

5.3.11 Positive and negative predictive values and sensitivity of the orbitofrontal morphology alone and in combination with the paracingulate variants

The positive and negative predictive values were calculated, as well as sensitivity and specificity of those conditions when one or both following structural markers in one subject were identified: the right and left orbitofrontal sulcogyral pattern type III and/or the left and right absent paracingulate sulcus variant. The orbitofrontal type III in the right and left hemisphere and the left and right absent paracingulate sulcus variant were chosen for these analyses as the distributions of both paracingulate sulcus and orbitofrontal patterns were found to be altered in patients with bipolar disorder. These values were estimated in individuals at high genetic risk of developing bipolar disorder.

The positive predictive value in this case was the proportion of those among the participants at high risk who developed depression with the right or left orbitofrontal type III and/or the left or right absent PCS.

The negative predictive value was the proportion of those among the participants at high risk without type III in the right or left hemisphere and/or the left or right absent PCS who remained well.

Sensitivity in this case was the probability that presence of the right or left orbitofrontal type III and/or the left or right absent PCS will indicate bipolar disorder among those with bipolar disorder.

Specificity was the fraction of those at high risk without bipolar disorder who will not have the right or left orbitofrontal type III and/or the left or right absent PCS.

5.3.11.1 The orbitofrontal type III in the right hemisphere:

	High risk ill	High risk well
Type III RH present	9	8
Type III RH absent	15	77

Positive predictive value = 9 / (9 + 8) * 100 = 52.9%
Negative predictive value = 77 / (15 + 77) * 100 = 83.7%
Sensitivity = 9 / (9 + 15) * 100 = 37.5%
Specificity = 77 / (8 + 77) * 100 = 90.6%

5.3.11.2 The orbitofrontal type III in the left hemisphere:

	High risk ill	High risk well
Type III LH present	9	13
Type III LH absent	15	72

Positive predictive value = 9 / (9 +13) * 100 = 40.9%

Negative predictive value = 72 / (15 + 72) * 100 = 82.8%

Sensitivity = 9 / (9 + 15) * 100 = 37.5%

Specificity = 72 / (13 + 72) * 100 = 84.7%

5.3.11.3 The left absent PCS variant:

	High risk ill	High risk well
Left PCS present	13	18
Left PCS absent	11	67

Positive predictive value = 13 / (13 + 18) * 100 = 41.9%

Negative predictive value = 67 / (11 + 67) * 100 = 85.9%

Sensitivity = 13/ (13 +11) * 100 = 54.2%

Specificity = 67 / (18 + 67) = 78.8%

5.3.11.4 The right absent PCS variant:

	High risk ill	High risk well
Right PCS present	13	48
Right PCS absent	11	37

Positive predictive value = 13 / (13 + 48) * 100 = 21.3%

Negative predictive value = 37 / (11 + 37) * 100 = 77.1%

Sensitivity = 13 / (13 +11) * 100 = 54.2%

Specificity = 37 / (48 + 37) = 43.5%

5.3.11.5 Present either type III in the right hemisphere or the left absent PCS variant or both of them:

It was important to examine whether combination of both distinctive features – the right orbitofrontal type III and the left absent PCS variant – will influence positive and negative predictive values, as well as sensitivity and specificity. If this is the case then it might support the idea of combining structural patterns into the system of markers to increase prediction of bipolar disorder in high risk individuals.

	High risk ill	High risk well
Type III or left PCS or both present	16	24
Type III or left PCS or both absent	8	61

Positive predictive value = 16 / (16 + 24) * 100 = 40%

Negative predictive value = 61 / (8 + 61) * 100 = 88.4%

Sensitivity = 16 / (16 + 8) * 100 = 66.7%

Specificity = 61 / (24 + 61) * 100 = 71.8%

5.3.11.6 Present either type III in the left hemisphere or the right absent PCS variant or both of them:

	High risk ill	High risk well
Type III or right PCS or both present	22	62
Type III or right PCS or both absent	2	23

Positive predictive value = 22 / (22 + 62) * 100 = 26.2%

Negative predictive value = 23 / (2 + 23) * 100 = 92.0%

Sensitivity = 22 / (22 + 2) * 100 = 91.7%

Specificity = 23 / (62 + 23) * 100 = 27.1%

5.3.11.7 Present either type III in the left hemisphere or the left absent PCS variant or both of them:

	High risk ill	High risk well
Type III or left PCS or both present	19	30
Type III or left PCS or both absent	5	55

Positive predictive value = 19 / (19 + 30) * 100 = 38.8%

Negative predictive value = 55 / (5 + 55) * 100 = 91.2%

Sensitivity = 19 / (19 + 5) * 100 = 79.2%

Specificity = 55 / (30 + 55) * 100 = 64.7%

5.3.11.8 Present either type III in the right hemisphere or the right absent PCS variant or both of them:

	High risk ill	High risk well
Type III or right PCS or both present	17	49
Type III or right PCS or both absent	7	36

Positive predictive value = 17 / (17 + 49) * 100 = 25.8%

Negative predictive value = 36 / (7 + 36) * 100 = 83.7%

Sensitivity = 17 / (17 + 7) * 100 = 70.8%

Specificity = 36 / (49 + 36) * 100 = 42.4%

5.4 Conclusion

In this chapter the orbitofrontal morphology and its association with the paracingulate sulcus, the symmetry - asymmetry scores and a gender effect on the orbitofrontal and anterior cingulate morphology were examined in the Bipolar Family Study. Neuropsychological scores, associations of the orbitofrontal sulcogyral patterns with brain volume, positive and negative predictive values and sensitivity tests were analysed in those at high risk of developing bipolar affective disorder.

Orbitofrontal cortex

There was an increased frequency of the orbitofrontal type III and the reduced expression of the orbitofrontal type I found in both right and left hemispheres in those at high risk who became ill. The distribution of the orbitofrontal patterns in those at high risk who became ill was similar to the distribution of the orbitofrontal patterns in patients with bipolar disorder from the Psychosis Study (see **Chapter 3** for details). Moreover, the OFC pattern distribution in those at high risk of developing bipolar disorder who remained well was similar to healthy controls (and similar to the orbitofrontal pattern distribution in the EHRS in controls and those at high risk of developing schizophrenia who remained well respectively, **Chapter 4**). Further, when a direct comparison was made between the high risk individuals who remained well and the high risk participants who became ill, a significant difference was found in the distribution of the orbitofrontal sulcogyral patterns with an increased frequency of type III and reduced frequency of type I in both right and left hemispheres in those high risk participants who became ill. This data suggests that a particular orbitofrontal sulcogyral pattern, type III, is associated with the development of bipolar disorder. On the contrary, people with type I have a reduced risk of this illness. Furthermore, the distribution of

type III in the left hemisphere could potentially distinguish patients with schizophrenia from individuals with bipolar disorder.

Similarly to the analysis in **Chapter 3** and **4**, a gender effect was examined in the BFS. As in the Psychosis Study (**Chapter 3**) and in the EHRS (**Chapter 4**), the differences in the distribution of the orbitofrontal type III in the right hemisphere seemed to be originated in males while the distribution of the orbitofrontal type III in the left hemisphere was more likely to be originated in females. Moreover, similarly to the findings in the Psychosis Study (patients with bipolar disorder and their unaffected relatives, **Chapter 3**) healthy controls and all high risk individuals were similar in distribution of symmetric and asymmetric scans.

Anterior Cingulate Cortex

Comparison of the ACC distribution between the groups revealed no difference in the distribution of the cingulate sulcus between the groups. There was no gender effect found on the distribution of the cingulate sulcus.

The distribution of the paracingulate sulcus variants in the left hemisphere differed between the groups by the increased frequency of the prominent paracingulate sulcus variant in the left hemisphere in the high risk group. Within the high risk groups those who remained well were more likely to have the prominent PCS. The direct gender analysis revealed that female high risk participants had a significantly increased frequency of the prominent PCS variant in both left and right hemispheres in high risk participants. It is noticeable that the paracingulate sulcus is likely to share the same gender effect in the left hemisphere as the orbitofrontal morphology in this study as well as in the Psychosis Study (See **Chapter 3** for details) and in the EHRS (**Chapter 4**).

Similar to the case of the orbitofrontal symmetry – asymmetry in patients with bipolar disorder and their unaffected relatives in the Psychosis Study (**Chapter 3)**, there was no difference found in the CS or PCS symmetry - asymmetry score between the groups with both genders included or separately either in males or in females.

Associations between OFC and ACC

There is an indication in this data that there could be a connection between the orbitofrontal and anterior cingulate morphology in the right and left hemispheres. For example, healthy individuals with type III in the left hemisphere were less likely to have the prominent paracingulate sulcus variant in the right hemisphere compared to those participants that were without the orbitofrontal type III in the left hemisphere. These results were more likely driven by male participants rather than by females (the same gender effect as for the distribution of the orbitofrontal sulcogyral patterns). Further, the participants at high risk of developing bipolar disorder with the orbitofrontal type III in the right hemisphere were more likely to have the paracingulate sulcus in the right hemisphere absent compared to those at high risk with any other orbitofrontal pattern. Furthermore, those high risk participants with type II in the right hemisphere were more likely to be in a possession of the prominent paracingulate sulcus variant in the left hemisphere as well. It was discovered that this difference was more likely to be found in females than in males. Moreover, those at high risk who became ill with type III in the left hemisphere were more likely to be in a possession of the present PCS variant in the right hemisphere. This association was found to be originated in males rather than in females.

Associations between cingulate and paracingulate sulcus were found either in the same hemisphere (between the right connected cingulate sulcus and the right present or prominent paracingulate sulcus in healthy controls), or

between the opposite hemispheres (the right connected cingulate sulcus and the left present paracingulate sulcus variant in healthy controls and in those at high risk who became ill).

Neuropsychological and clinical associations of the orbitofrontal cortex

The analysis revealed that male participants with the orbitofrontal type III in the right hemisphere scored less in the verbal IQ than those with any other type in the right hemisphere. Similarly, participants with the orbitofrontal type III in the left hemisphere scored less in the verbal IQ than those with any other type in the left hemisphere.

Participants with the orbitofrontal type I in the right hemisphere experienced some difficulties at the beginning of the IDED task. Male high risk participants of developing bipolar disorder with the orbitofrontal type II in the right hemisphere performed better during the IDED task than male participants without type II in the right hemisphere making fewer errors and, therefore, requiring less trials to complete the stage. The participants with a high risk of developing bipolar disorder with the orbitofrontal type III in the right hemisphere experienced difficulties during reversal stages of the IDED task making more errors and, therefore, requiring more reversal trials to complete the stage. Participants with the orbitofrontal type I in the left hemisphere were the best performers during extra-dimensional stage, while those at high risk of developing bipolar disorder with type II in the left hemisphere experienced greater difficulties during extra-dimensional reversal stage. Those with type III in the left hemisphere had problems while performing the intra-dimensional set-shifting stage at the beginning of the IDED task.

Moreover, those with type III in the right hemisphere experienced difficulties while performing during medium high constraint of the Hayling Sentence Completion Task. Those at high risk of developing bipolar disorder with type I

in the right hemisphere performed poorly during medium low constraint. Participants with type II in the right hemisphere performed better during medium low constraint (both males and females) and medium high constraint (males). The female high risk participants of developing bipolar disorder with the orbitofrontal type III in the left hemisphere performed poorer than female individuals with any other type in the left hemisphere. On the contrary, the male high risk participants of developing bipolar disorder with the orbitofrontal type III in the left hemisphere performed better during low constraint, medium high constraint and high constraint than male individuals with any other type in the left hemisphere.

There were interesting associations found between the orbitofrontal patterns and the personality and temperamental traits. The high risk participants of developing bipolar disorder with the orbitofrontal type I in the right hemisphere scored more in irritability. The female high risk participants of developing bipolar disorder with the orbitofrontal type II in the right hemisphere scored less in cyclothymia and depression. The male high risk participants of developing bipolar disorder with the orbitofrontal type III in the right hemisphere scored less in openness to experience and were less able to identify sadness as a face expression than male individuals with any other type in the right hemisphere. The female high risk participants of developing bipolar disorder with the orbitofrontal type I in the left hemisphere scored more in openness, hyperthymia and irritability, and less in agreeableness (a tendency to feel compassionate towards others) than female individuals with any other type in the left hemisphere. The female high risk participants of developing bipolar disorder with the orbitofrontal type II in the left hemisphere scored less in irritability and hyperthymia, and more in agreeableness than female individuals with any other type in the left hemisphere. The participants with a high risk of developing bipolar disorder with the orbitofrontal type III in the left hemisphere scored more in conscientiousness (originated in the female participants), less in openness (originated in the male participants),

and more in neuroticism than individuals with any other type in the left hemisphere.

The female participants at high risk of developing bipolar disorder with the orbitofrontal type III in the right hemisphere scored more in the HRSD than the female individuals with any other type in the right hemisphere. The high risk participants of developing bipolar disorder with the orbitofrontal type I in the left hemisphere scored more in the YMRS than individuals with any other type in the left hemisphere. This is an interesting finding given that the participants also scored more in hyperthymia and irritability.

Similar to the results in the EHRS (**Chapter 4**), the orbitofrontal type II in the right hemisphere was found to be associated with the RISC scores in such a way that those at high risk of developing bipolar disorder with type II in the right hemisphere scored less in the RISC compared to those high risk participants who were without type II in the right hemisphere.

As in the EHRS (**Chapter 4**), the orbitofrontal patterns were also found to be associated with volumes of various brain regions. For example, similar to the EHRS participants at high risk of developing bipolar disorder without orbitofrontal type I in the right hemisphere had larger volume of the temporal lobe. Additionally, female participants at high risk with the orbitofrontal type I in the right hemisphere had smaller volume of the right superior frontal gyrus compared to those female individuals at high risk with any other orbitofrontal pattern in the right hemisphere. Male participants at high risk with the orbitofrontal type I in the right hemisphere had smaller volume of the left middle temporal gyrus, larger volume of the isthmus of the cingulate gyrus in the right hemisphere and smaller volume of the left medial orbitofrontal gyrus compared to those male individuals at high risk with any other orbitofrontal pattern in the right hemisphere. Again similar to the results in the EHRS, participants at high risk of developing bipolar disorder without the

orbitofrontal type II in the right hemisphere had smaller volume of the left middle temporal lobe. As in the EHRS this difference was originated in males. Additionally, male participants at high risk with the orbitofrontal type II in the right hemisphere had larger volume of the left medial orbitofrontal cortex compared to those male individuals at high risk with any other orbitofrontal pattern in the right hemisphere. Participants at high risk with the orbitofrontal type III in the right hemisphere had a larger volume of the isthmus of the cingulate gyrus in the left hemisphere compared to those at high risk with any other orbitofrontal pattern in the right hemisphere. Participants at high risk with orbitofrontal type I in the left hemisphere had larger volume of the right rostral middle frontal cortex, larger left posterior cingulate and larger left frontal pole compared to those at high risk with any other orbitofrontal pattern in the hemisphere. This difference originated in females. Participants at high risk of developing bipolar disorder with the orbitofrontal type II in the left hemisphere had smaller volume of the right and left rostral middle frontal cortex compared to those at high risk with any other orbitofrontal pattern in the left hemisphere. This difference also originated in females. Those at high risk with the orbitofrontal type III in the left hemisphere had smaller volume of the left posterior cingulate cortex and left frontal pole compared to those at high risk with any other orbitofrontal pattern in the left hemisphere. These findings show associations between orbitofrontal patterns and volumes of the brain regions that represent parts of the orbitofrontal network. Moreover, it becomes clearer that the same orbitofrontal patterns in the left and right hemisphere might have different characteristics.

The calculated negative predictive value for the orbitofrontal type III in the right hemisphere was almost as in the EHRS: 83.7% (89.9% in the EHRS). The calculated negative predictive value for the orbitofrontal type III in the left hemisphere was 82.8%. The calculated negative predictive value for the absent paracingulate sulcus variant in the left hemisphere was 85.9%.

Combination of both the orbitofrontal type III in the right hemisphere and the left absent paracingulate sulcus variant resulted in the increased negative predictive value 88.4%. Combination of both the orbitofrontal type III in the left hemisphere and the right absent paracingulate sulcus variant resulted in the increased negative predictive value 92.0%. So, combination of the right type III and the left paracingulate sulcus provides the best negative predictive value in those at high risk of developing schizophrenia (see **Chapter 4** for details). In a contrary, combination of the left type III and the right paracingulate sulcus gives the best negative predictive value in those at high risk of developing bipolar disorder. This suggests once again importance of the left orbitofrontal cortex in pathophysiology of bipolar disorder. Supporting this, combination of both the orbitofrontal type III in the left hemisphere and the left absent paracingulate sulcus variant resulted in the negative predictive value of 91.2%, while combination of both the orbitofrontal type III in the right hemisphere and the right absent paracingulate sulcus variant resulted in the negative predictive value of 83.7%. These findings demonstrate the importance of the orbitofrontal sulcogyral patterns and the paracingulate sulcus for predictability of bipolar disorder in the high risk population.

These results will be further discussed in details in Chapter 8.

Chapter 6

Brain structure differences associated with orbitofrontal morphology in healthy controls

This chapter describes differences in brain structure that were found to be associated with various orbitofrontal sulcogyral patterns in healthy individuals. Grey matter density was compared using Voxel - Based Morphometry analysis. Cortical thickness on the various areas of the frontal lobe was extracted using the FreeSurfer software. Cortical thickness in healthy individuals with different orbitofrontal sulcogyral patterns was analysed using ANOVA. Healthy individuals with the orbitofrontal type III had reduced grey matter density and cortical thickness in the frontal region compared to those with the orbitofrontal type I.

6.1 Introduction

The orbitofrontal sulcogyral patterns (Chiavaras and Petrides, 2000; Chakirova *et al.,* 2010) were previously found altered in patients with schizophrenia represented by the reduction of the orbitofrontal type I and an increased frequency of type III in the right hemisphere (Nakamura *et al.,* 2007). In the present study we have analyzed grey matter density and cortical thickness in healthy individuals with the orbitofrontal type I, II or type III in both left and right hemispheres exploring an impact of sulcogyral patterns on these measures.

6.2 Methods

Eighty two healthy controls were recruited, scanned and underwent a neuropsychological assessment as a part of the longitudinal Bipolar Family Study. The orbitofrontal cortex sulcogyral patterns in each hemisphere of the participants were rated according to the existing classification (Chiavaras and Petrides, 2000; Chakirova *et al.,* 2010). Only those individuals that had the same orbitofrontal type in the right and left hemispheres were selected and examined for grey matter density by applying Voxel - Based Morphometry using the SPM5 software (Statistical Parametric Mapping http://www.fil.ion.ucl.ac.uk/spm/software/spm5), running in Matlab (http://www.mathworks.co.uk/products/matlab), and for cortical thickness on the various areas of the frontal lobe using the FreeSurfer software (v. 4.05) package (http://surfer.nmr.mgh.harvard.edu).

6.2.1 Participants

Participants for this study were recruited as part of the large and longitudinal Bipolar Family Study, intended to examine and follow up those at high genetic risk of developing bipolar disorder. At the beginning, patients with bipolar I disorder were identified from the case loads of psychiatrists across Scotland. They were asked to identify members of their close family (first or second degree relatives) aged 16 - 25 and to authorize either a review of their case notes, or a structural clinical interview. The diagnosis of all participants affected was confirmed with either the OPCRIT symptom checklist (McGuffin *et al.,* 1991) or the structured clinical interview for DSM-IV (SCID) (First *at al.,* 2002).

Unaffected relatives of the probands with at least one first - degree or two second - degree relatives with bipolar I disorder were invited to participate in the study. Healthy control subjects with no personal or family history of

bipolar disorder were recruited from the social networks of the high-risk subjects themselves. Both groups did not differ on age, sex or IQ (See **Figure 5.1** in **Chapter 5**). Exclusion criteria for both groups were a personal history of major depression, mania or hypomania, any major neurological disorder, a history of substance dependence, a history of learning disability or any history of head injury that included loss of consciousness and also any contraindications to MRI examination. All participants signed written consent and the study was approved by committee A of the Multi-centre Regional Ethics Committee for Scotland.

6.2.2 Clinical assessments

The lifetime absence of affective disorders, schizoaffective disorder and schizophrenia was confirmed using the structural clinical interviews for DSM-IV (SCID). Current manic and depressive symptoms were rated using the Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HDRS) respectively (See **Chapter 5** for the details on clinical assessment). Detailed information about lifetime alcohol and drug use was also obtained.

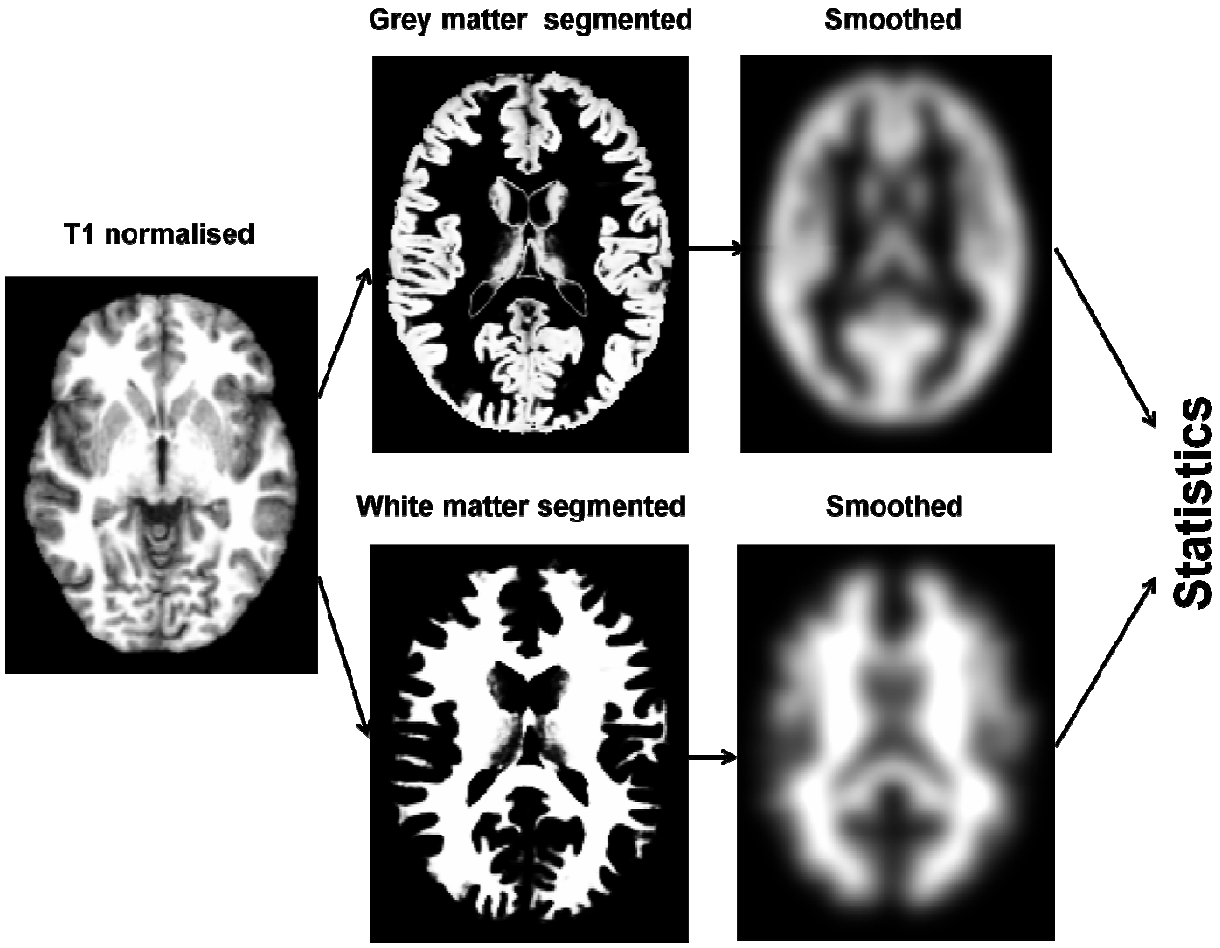
The TEMPS-A, a validated 39 item questionnaire providing measurement along five dimensions, was applied to assess estimates of temperamental variations in minor affective symptoms.

6.2.3 Voxel-Based Morphometry (VBM) analysis

VBM is a well known automated neuroimaging analysis technique that was developed to investigate regional differences in anatomy of the brain on T1 - weighted MRI scans between groups of subjects (See **Figure 6.1**). This method is unbiased, analyzes the whole brain and does not require any priory hypothesis about which structure of the brain might be involved. It applies the general linear model (GLM) using SPM (Statistical Parametric

Mapping; http://www.fil.ion.ucl.ac.uk/spm) software and requires a series of pre - processing steps. General pre - processing steps of VBM analysis are segmentation, normalization and smoothing. During segmentation, anatomical scan is segmented into the gray matter, white matter and cerebro - spinal fluid (CSF). During spatial normalization, every brain is registered to a template. This allows excluding most of the large differences in brain anatomy among participants by deforming brain according to determined parameters to fit a template. At this stage the segmented brain images can be modulated or left unmodulated. Modulation allows preserving the total amount of tissue in the image by correcting for volume change that occurred during the spatial normalization step. Modulated images are necessary to examine the volume changes while unmodulated images allow analysing only differences in concentration (or density). Then, the brain images are smoothed. By this technique each voxel represents the average of itself and its neighbours. Finally, the images are compared between the groups by performing standard parametric statistical tests (*t* - tests or F - tests) across brains at every voxel. VBM in SPM5 that were used in this study applies a Hidden Markov random field (HMRF) model to reduce noise. The significance of any difference is estimated by application of Gaussian random fields.

Figure 6.1. The VBM analysis and its pre - processing steps. The CSF was excluded from this study.



6.2.4 Cortical thickness

MRI - based analysis of cortical thickness was performed using the FreeSurfer software (v. 4.05) package (http://surfer.nmr.mgh.harvard.edu). The methodology has been previously described elsewhere (Dale *et al.,* 1999; Fischl *et al.,* 1999 a, b; Fischl and Dale, 2000; Han *et al.,* 2006). In brief, processing on the FreeSurfer cortical thickness pipeline involves

intensity normalisation, registration to Talairach space, skull stripping, segmentation of white matter, tessellation of the white matter boundary, smoothing of the tessellated surface and automatic topology correction.

Intensity normalization is used to correct the variations of intensity due to magnetic field inhomogeneities. A normalised intensity images are created from T1 - weighted MRI scans. Then the volumes are registered with the Talairach (Talairach and Tournoux, 1988) using the automated Talairach registration procedure to compute the transformation parameters. This procedure maximizes the correlation between an average volume and the individual volume and allows computing seed points in later stages. The skull stripping is also an automated procedure that involves deforming a tessellated ellipsoidal template into the shape of the inner surface of the scull. This deformed template is used to extract the brain from the scull by removing all voxels outside the tessellated surface from the MRI volume. The segmentation of white matter in FreeSurfer is a two-step procedure and requires classification of voxels as white matter or something other than white matter. This step is based on intensity and neighbour constraints. The computed cutting planes (their location is determined by the localization of the corpus callosum and pons, which is estimated during Talairach registration procedure) are used to separate hemispheres and to remove brain stem and cerebellum. After that the volume is examined to identify regions that contain more than one tissue type with any interior holes in the components representing white matter that must be filled. Tessellation of the white matter boundary produces an accurate representation of the grey and white matter interface and a pial surface. The tessellated surface is then smoothed. The topological defects (such as a single - voxel ‘bridge’ across a sulcus) are examined and removed manually.

The cortical thickness measurement could be obtained as a distance between the white and pial surfaces. The measurements of cortical thickness

were obtained via reconstruction of representations of the grey and white matter boundaries and the cortical surface using continuity and intensity information from the entire 3D MRI volume. The distance between the white and pial surfaces was calculated individually for each scan at each point across the cortical mantle.

The smoothing was done by application of a circularly symmetric Gaussian kernel across the cortical surface. A standard deviation of 12.6 mm was used. In order to align cortical folding patterns maps were averaged across participants using a non - rigid high - dimensional spherical averaging method. This technique allows an accurate match of morphologically homologous cortical regions among participants and therefore, an accurate measure of cortical thickness.

The regions that demonstrated significant morphological changes by VBM were used to create regions of interest (ROIs) on a standard brain. They were mapped back then to each individual subject by applying spherical morphing in order to identify homologous regions across subjects. After that a mean thickness score over each location was calculated for every participant and used for further analysis.

For each hemisphere, differences in cortical thickness between groups of participants with different orbitofrontal sulcogyral pattern were examined by comparing a mean thickness score of cortical thickness in the regions of interest in every group of participants applying non - parametric two - sample *t* - test. As we had only three groups our comparisons were limited by three tests only.

6.2.5 MRI acquisition and analysis

The MRI scans of the participants were obtained using a 1.5 - T GE MRI scanner (GE Medical Systems, Milwaukee, Wisconsin). In order to image the whole brain midline sagittal localization was followed by two further sequences. The first sequence was a transverse spin - echo scan, which acquired both T_2 - and proton density – weighted images of the brain for clinical reporting by a consultant neuroradiologist. The final sequence was a coronal gradient echo sequence with magnetization preparation and produced 128 coronal high - resolution T_1 - weighted images, which were used for structural image analysis (time of inversion [TI] = 600 msec, echo time = 3.4 msec, flip angle = 15^o, field of view = 22, slice thickness = 1.7 mm, matrix = 256 x 192). Images were converted into NIFTI file format for further processing.

The Statistical Parametric Mapping package (SPM5; The Wellcome Department of Imaging Neuroscience, University College London), running in Matlab version 7.1 (The Math Works, Natick, MA) was used to process scans. Firstly, we employed the default segmentation supplied by SPM5. All scans were segmented using study specific a priori tissue maps (Good *at al.,* 2001; Moorhead *et al.,* 2004). Then, we recovered unmodulated grey matter density profiles in MNI space. Finally, the grey matter segmentations were smoothed using a 12 - mm full - width at half maximum (FWHM) Gaussian kernel (Ashburner and Friston, 2000).

6.2.6 Method of identification of orbitofrontal sulcogyral patterns

The identification protocol of orbitofrontal sulcogyral patterns has been previously described elsewhere (Chiavaras and Petrides, 2000; Nakamura *et al.,* 2007; Chakirova *et al.,* 2010; See also **Chapter 1** and **Chapter 3** for details). In brief, the orbitofrontal sulcogyral patterns were classified on the

basis of the continuity of the main orbital sulci: lateral and medial orbital sulci through the transverse orbital sulcus. The pattern was named as type I if the rostral and caudal parts of the lateral orbital sulcus were connected and the rostral part of the medial orbital sulcus was disconnected from the transverse orbital sulcus. If the rostral and caudal parts of the lateral and medial orbital sulci were connected this pattern was called 'type II'. If both lateral and medial orbital sulci were disconnected the pattern was named 'type III'. There was also type IV with connected medial and disconnected lateral orbital sulci. The MRIcro software (http://www.mccauslandcenter.sc.edu/mricro/mricro/mricro.html) was used to identify and classify the orbitofrontal sulcogyral patterns.

6.2.7 Statistics

Only healthy controls with type I, II and III in the right hemisphere were included in this study. A scan was defined as symmetric if it possessed the same orbitofrontal pattern in the left and the right hemisphere (type I – type I or type II – type II and etc). Following the absence of the scans with the type IV symmetry we formed three groups only: controls with type I in both hemispheres (30 scans), controls with type II in both hemispheres (10 scans) and controls with type III in both hemispheres (5 scans).

The brain extraction from the non - brain tissue, normalisation and segmentation of T1s into the grey and white matters were performed using created in Matlab and C-scripts written by Dr. Moorhead at the Division of Psychiatry for SPM5. After segmentation, the registration was checked using the 'Check Reg' function of the SPM5 software before smoothing scans. The smoothing was performed using 'Smooth' function of SPM5. Then, smoothed unmodulated grey and white matter images were entered into further statistical analyses in SPM5 (www.fil.ion.ucl.ac.uk/spm) where two - sample *t* - tests were performed comparing groups 1, 2 and 3 with the orbitofrontal

type I, II or III in both hemispheres accordingly. Covariation for handedness, gender and NART IQ, implicit and explicit masking were specified in the factorial design. Results were reported for contiguous clusters of voxels of uncorrected significance of p = 0.005 or less, where the cluster - corrected p - value was less than 0.05 using the cluster toolbox 'ns' (Hayasaka *et al.,* 2004; Moorhead *et al.,* 2005) specifically developed for structural image analysis. Only clusters larger than 50 voxels were reported.

6.3 Results

The main comparison is between participants with the orbitofrontal type III and the orbitofrontal type I, considering predictive value of the orbitofrontal type III in the right hemisphere in those at high genetic risk of developing schizophrenia (Nakamura *et al.,* 2007; Chakirova *et al.,* 2010; See **Chapter 4** for details).

6.3.1 Participants

Overall eighty two healthy volunteers were recruited as a part of the longitudinal Bipolar Family Study, although only forty of them had symmetric scans with the orbitofrontal type I, II or III in the right or in the left hemisphere. None of the individuals fulfilled the DSM - IV criteria for a current or previous mood or psychotic episode, anxiety disorder or substance dependence. The demographic characteristics of healthy individuals with different orbitofrontal patterns (symmetric scans) are shown in **Figure 6.2**. The groups did not differ significantly in age, gender, handedness or IQ.

Figure 6.2. The demographic characteristics of healthy participants with different orbitofrontal patterns (symmetric scans).

	Type I (No)	Type II (No)	Type III (No)	F	df	P value
Age (mean (SD))	20.478 (2.0549)	20.523 (2.0600)	20.220 (3.6451)	0.032	2	**0.969**
NART IQ (mean (SD))	108.19 (8.537)	114.67 (5.979)	108.20 (5.891)	2.406	2	**0.104**
				Pearson Chi-square	df	**P value**
Gender (m : f)	13 : 13	3 : 6	1 : 4	1.944	2	**0.378**
Handedness (R : L : B)	**21 : 4 : 1**	**9 : 0 : 0**	**5 : 0 : 0**	**1.177**	**2**	**0.319**

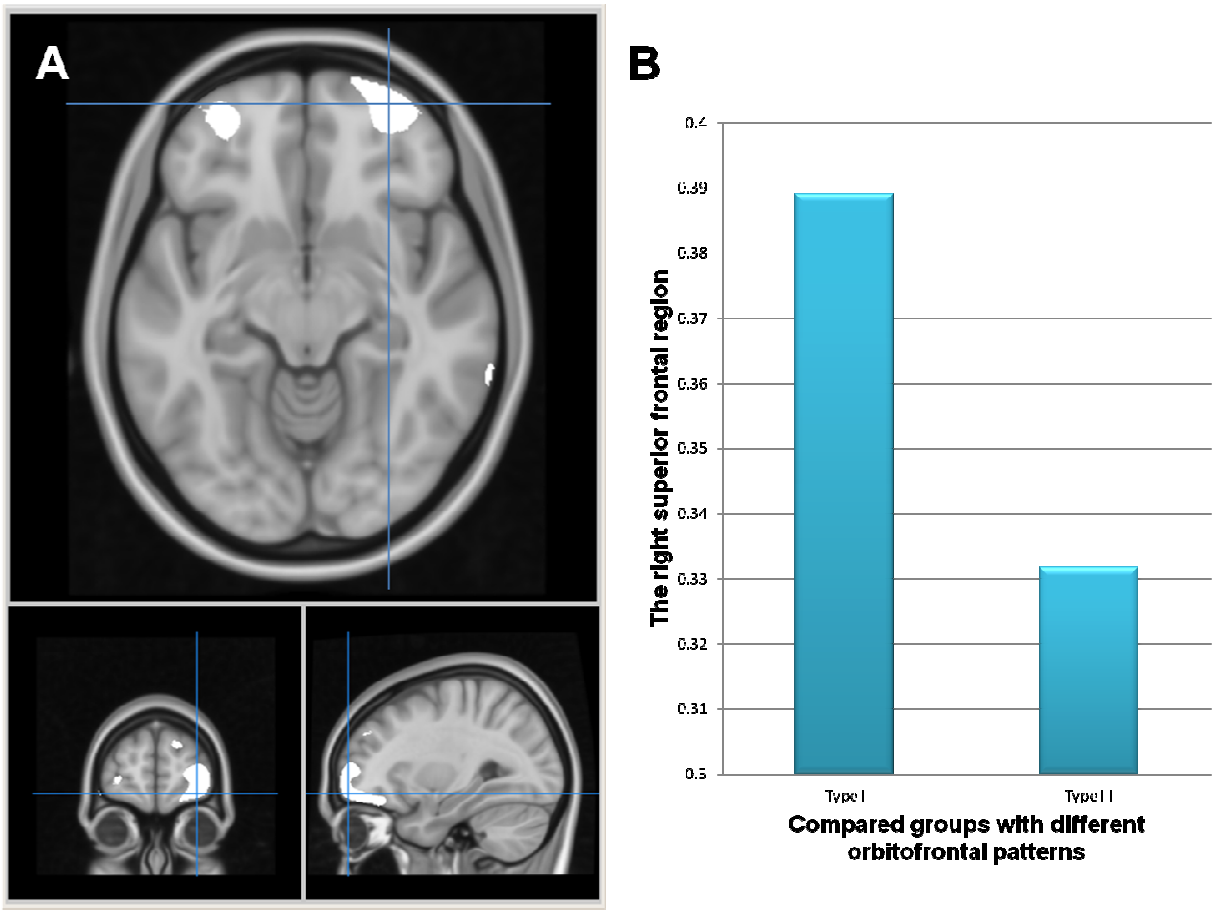
6.3.2 Comparison of controls with different orbitofrontal patterns

Type I versus Type III (See Figure 6.3)

Healthy individuals with the orbitofrontal type III in both hemispheres had significantly reduced grey matter density in the right orbitofrontal cortex compared to healthy volunteers with the orbitofrontal type I in both hemispheres (MNI coordinates of the maximum voxel: x = 30, y = 61, z = -11; K voxel = 4400, T = 4.54, Z = 3.88, p corrected non-stationary = 0.008; See **Figure 6.3**). This cluster (BA 10) included the right superior frontal and middle frontal gyri. In order to analyse from what hemisphere this difference has originated the distribution of the orbitofrontal sulcogyral patterns was additionally compared between those healthy participants who possessed the orbitofrontal types I and III in the right or in the left hemisphere only (healthy individuals with the asymmetric as well as symmetric orbitofrontal morphology). This analysis demonstrated that the cluster was derived from

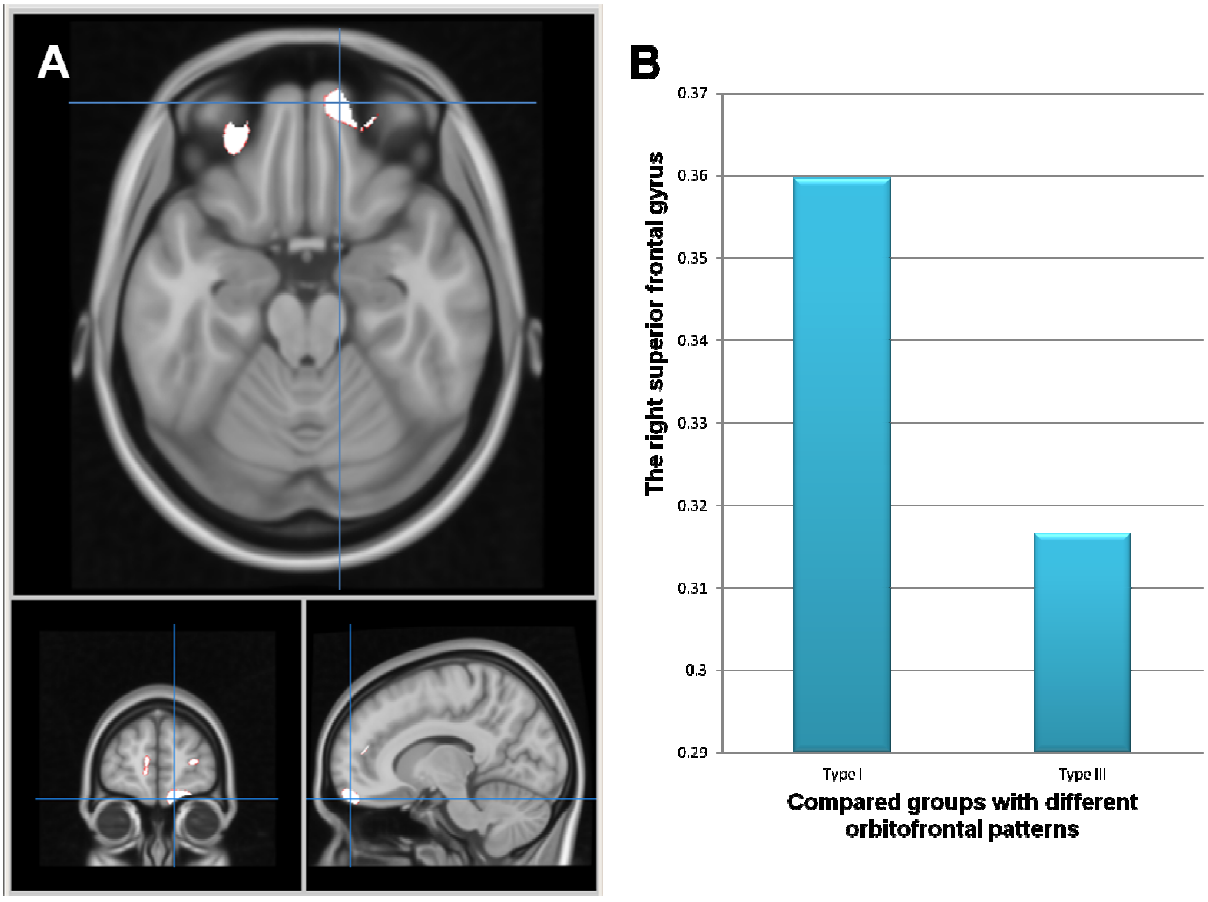
the right hemisphere comparison. When corrected for gender, handedness and the NART IQ scores the cluster subdivided into two smaller clusters:

Figure 6.3. The area of significant grey matter density difference between healthy participants with the orbitofrontal type I and healthy individuals with the orbitofrontal risk - type III. **(A)** The localization of the cross is pointed at the maximum voxel (the right superior frontal gyrus; x = 30, y = 61, z = - 11; BA 10) where participants with the orbitofrontal type III showed reduced grey matter density compared to the individuals with the orbitofrontal type I. Cluster is significant at $p < 0.05$. **(B)** Graph demonstrates extracted values from Statistical Parametric Mapping for the right superior frontal cluster (type I versus type III). See text for further details.



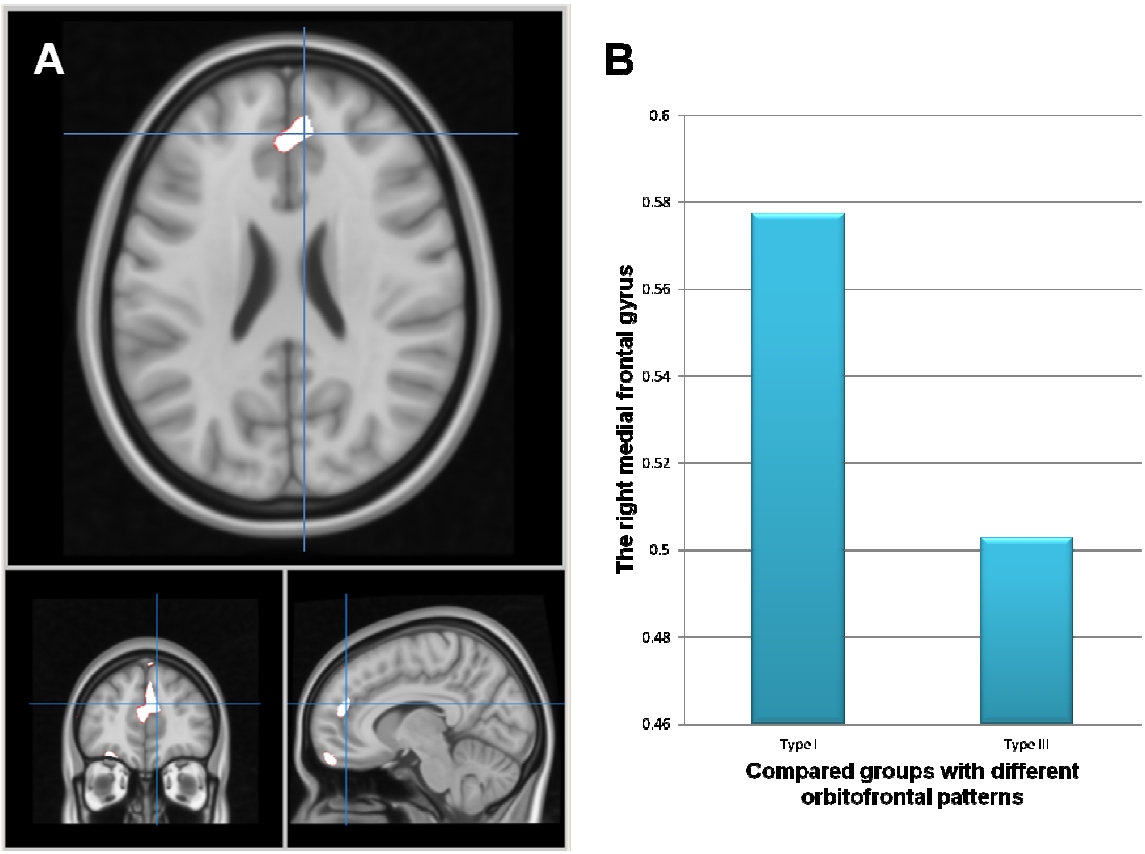
1. The right superior frontal gyrus (BA 10) (MNI coordinates of the maximum voxel: x = 15, y = 60, z = - 21; K voxel = 543, T = 3.95, Z = 3.61, p corrected non - stationary = 0.046; See **Figure 6.4**);

Figure 6.4. The area of significant grey matter density difference between healthy participants with the orbitofrontal type I and healthy individuals with the orbitofrontal risk - type III. **(A)** The localization of the cross is pointed at the maximum voxel (the right superior frontal gyrus; x = 15, y = 60, z = - 21; BA 10) where participants with the orbitofrontal type III showed reduced grey matter density compared to the individuals with the orbitofrontal type I. Cluster is significant at $p < 0.05$. **(B)** Graph demonstrates extracted values from Statistical Parametric Mapping for the right superior frontal gyrus (type I versus type III). See text for further details.



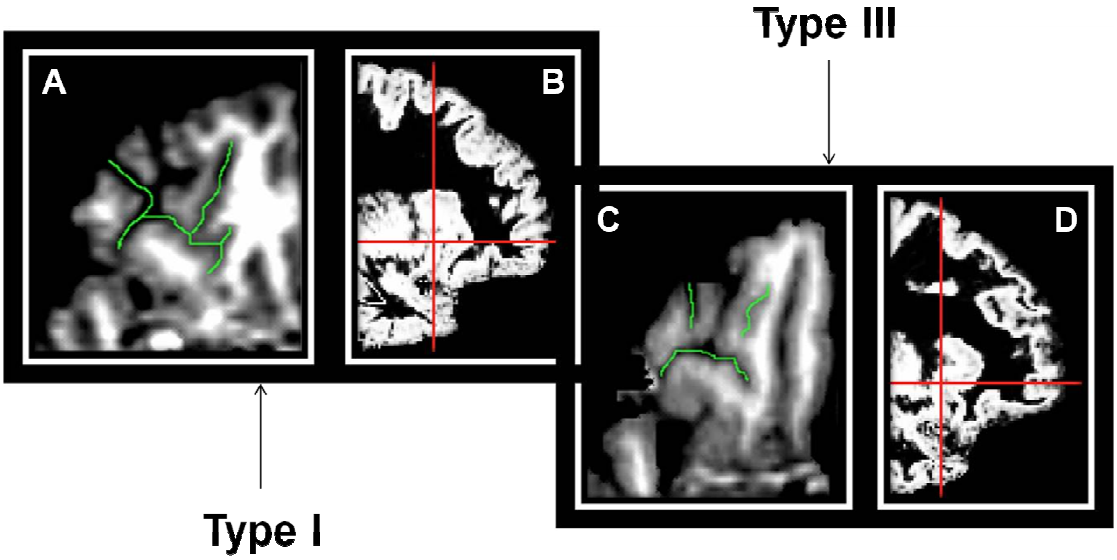
2. The right medial frontal gyrus (BA 9), the left and right anterior cingulate regions (BA 32) (MNI coordinates of the maximum voxel: x = 10, y = 46, z = 23; K voxel = 1182, T = 3.95, z = 3.60, p corrected non-stationary = 0.029; See **Figure 6.5**).

Figure 6.5. The area of significant grey matter density difference between healthy participants with the orbitofrontal type I and healthy individuals with the orbitofrontal risk - type III. **(A)** The localization of the cross is pointed at the maximum voxel (the right medial frontal gyrus; x = 10, y = 46, z = 23; BA 9) where participants with the orbitofrontal type III showed reduced grey matter density compared to the individuals with the orbitofrontal type II. Cluster is significant at $p < 0.05$. **(B)** Graph demonstrates extracted values from Statistical Parametric Mapping for the right medial frontal gyrus (type I versus type III). See text for further details.



Participants with type III in the right hemisphere had also reduced cortical thickness (F = 4.756, p = 0.012) in the right medial orbitofrontal area compared to controls with the orbitofrontal type I in the right hemisphere (See **Figure 6.6**). The data on cortical thickness was extracted using the FreeSurfer software (v. 4.05) package (http://surfer.nmr.mgh.harvard.edu).

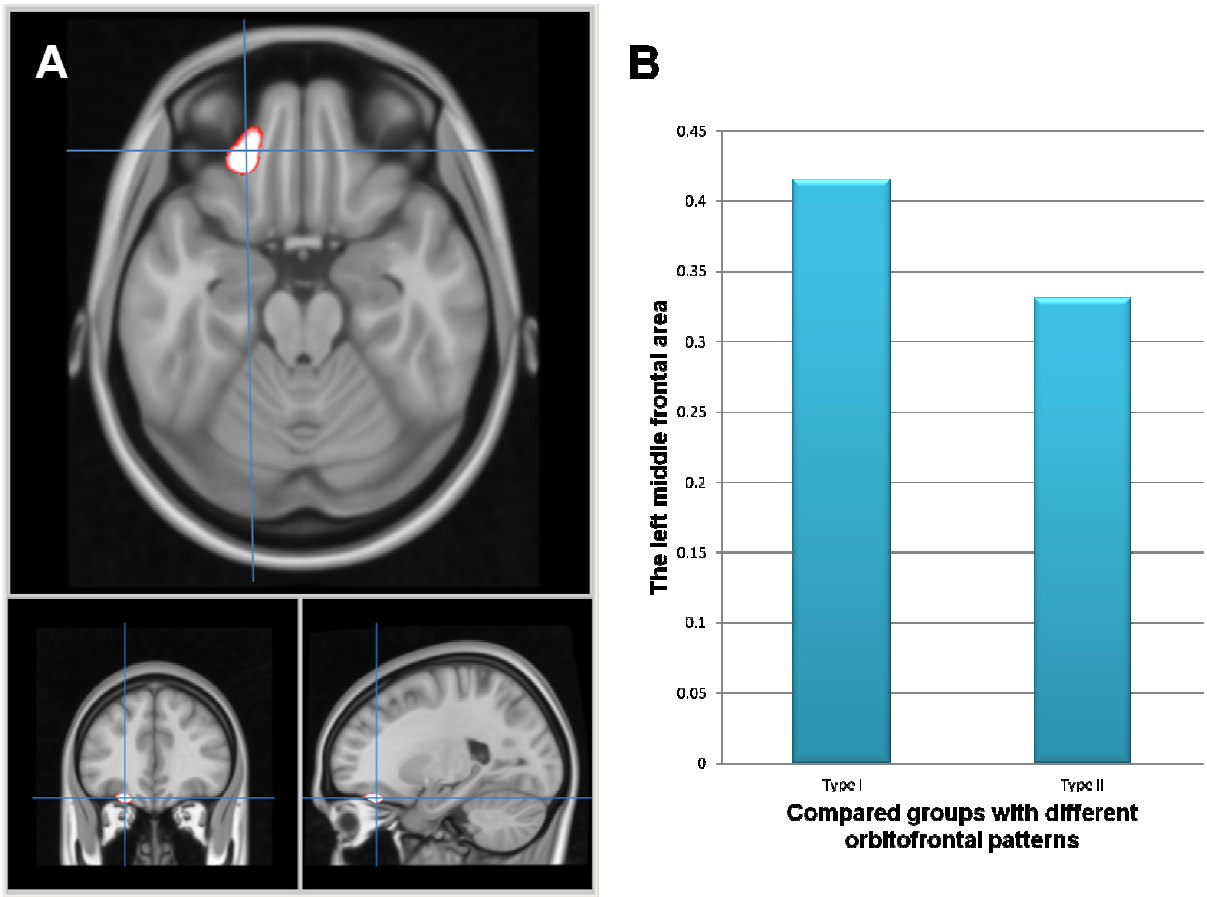
Figure 6.6. Grey tissue qualitative assessment in healthy individuals with the orbitofrontal type I versus healthy participants with the orbitofrontal type III. (A) The orbitofrontal area and a sulcogyral pattern (coloured in green) of a healthy participant with type I. (B) Extracted grey matter (frontal lobe) of a healthy participant with the orbitofrontal type I. (C) The orbitofrontal area and a sulcogyral pattern (coloured in green) of a healthy participant with type III. (D) Extracted grey matter (frontal lobe) of a healthy participant with the orbitofrontal type III. This figure demonstrates a visually detectable grey matter reduction in the participant with the orbitofrontal type III compared to a subject with the orbitofrontal type I. This qualitative assessment provides confirmation for the VBM analysis.



Type I versus Type II

Healthy participants with the orbitofrontal type II in both hemispheres had significantly reduced proportion of the grey matter in the left orbitofrontal cortex compared to those healthy individuals with the orbitofrontal type I in both hemispheres (MNI coordinates of the maximum voxel: x = - 22, y = 36, z = - 21; K voxel = 1719, T = 4.81, z = 4.16, p corrected non-stationary = 0.040; See **Figure 6.7**). This cluster included the following brain structures: the left middle frontal gyrus (BA 11), superior frontal gyrus (BA 11) and inferior frontal gyrus (BA 47). The origin of this cluster was analyzed by comparing those participants with the orbitofrontal types I and II in the right or left hemisphere. It appears that this difference originates from the right hemisphere comparison where this cluster was present as a region of significant difference and survived covariating for gender, handedness, and the NART IQ scores with improved p corrected non-stationary = 0.012 (K voxel = 1327, T = 4.00, Z = 3.71, close to the previous MNI coordinates of the maximum voxel: x = - 22, y = 38, z = - 23). As in case with symmetric scans, healthy individuals with the orbitofrontal type II in the right hemisphere had significantly reduced proportion of the grey matter in the left orbitofrontal cortex compared to those healthy volunteers with the orbitofrontal type I.

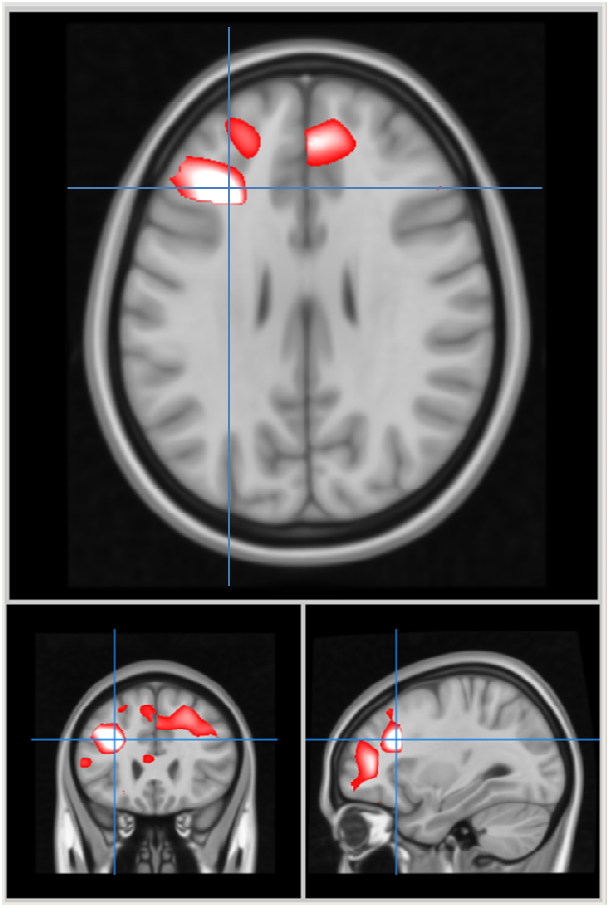
Figure 6.7. The area of significant grey matter density difference between healthy participants with the orbitofrontal type I and healthy individuals with the orbitofrontal type II. **(A)** The localization of the cross is pointed at the maximum voxel (the left middle frontal gyrus; x = - 22, y = 36, z = - 21; BA 11) where participants with the orbitofrontal type II showed reduced grey matter density compared to the individuals with the orbitofrontal type I. Cluster is significant at $p < 0.05$. **(B)** Graph demonstrates extracted values from Statistical Parametric Mapping for the left middle frontal area (type I versus type II). See text for further details.



Participants with the orbitofrontal type II in the left hemisphere had reduced white matter density in the middle frontal gyrus compared to healthy

individuals with type I in the left hemisphere (MNI coordinates: x = - 30, y = 25, z = 27; K voxel = 1182, p corrected non-stationary = 0.025, T = 4.62, Z = 4.12). This cluster (see **Figure 6.8**) included the white matter underlying the left middle frontal gyrus (BA 9).

Figure 6.8. The area of significant white matter density difference between healthy participants with the orbitofrontal type I and healthy individuals with the orbitofrontal type II. The localization of the cross is pointed at the maximum voxel (the left middle frontal gyrus; x = - 30, y = 25, z = 27; BA 9) where participants with the orbitofrontal type II showed reduced white matter density compared to the individuals with the orbitofrontal type I. Cluster is significant at $p < 0.05$.



Type II versus Type III

There was no difference found in proportions of the grey matter between controls with the orbitofrontal type II and type III.

6.4 Conclusion

Structural abnormalities associated with the orbitofrontal morphology were examined in healthy participants from the Bipolar Family Study who were without a family or personal history of mental illnesses, a history of brain injury or drug addiction. Those participants were subdivided into groups according to the type of the orbitofrontal pattern in both right and left hemisphere (symmetric scans; See **Chapter 1** and **Chapter 3** for details). Additionally, healthy individuals were subdivided on the basis of the distribution of the orbitofrontal sulcogyral types in the right or in the left hemisphere separately in order to analyse whether the results from symmetric scans were originated from the orbitofrontal morphology differences in particular hemispheres.

The grey matter density was compared in those forty healthy volunteers who possessed the orbitofrontal types I, II and III in both left and right hemispheres. This comparison revealed that healthy individuals with the orbitofrontal type III had reduced grey matter density in the right orbitofrontal area (the superior (BA 10) and middle frontal (BA 10) gyri), the right medial frontal gyrus (BA 9), the left and right anterior cingulate regions (BA 32), and that these results originated from the grey matter differences associated with the orbitofrontal morphology in the right hemisphere. Importantly, these VBM findings were supported by the reduction of cortical thickness in the right medial orbitofrontal area in the participants with type III in the right hemisphere compared to healthy volunteers with the orbitofrontal type I.

Healthy individuals with the orbitofrontal type II in both hemispheres had reduced grey matter density in the left orbitofrontal cluster that included the left middle frontal gyrus (BA 11), superior frontal gyrus (BA 11) and inferior frontal gyrus (BA 47), when compared to those controls with the orbitofrontal type I. This cluster was originated in those participants with the orbitofrontal

type II in the right hemisphere and survived covariation for gender, handedness and the NART IQ scores. Furthermore, healthy individuals with the orbitofrontal type II in the left hemisphere had reduced white matter density in the middle frontal gyrus when compared to healthy individuals with type I in the left hemisphere.

There was no difference found in the grey matter density when controls with the orbitofrontal type II and type III were compared.

This research is relatively novel as at the best of our knowledge the only publication on this field was done by Nakamura and colleagues (2008). The authors introduced new parcellation method of the orbitofrontal cortex and reported the smaller middle orbital gyrus in the schizophrenia group. However, this group did not find associations between the orbitofrontal patterns and parcellated brain volumes (Nakamura *et al.,* 2008). In the present study the VBM analysis was used instead of the parcellation method to examine grey matter differences between healthy controls possessing various orbitofrontal sulcogyral patterns. Importantly, unlike in the research published by Nakamura and colleagues (2008), only those healthy individuals who possessed the same orbitofrontal pattern in both hemispheres (symmetric scans) were examined. Further, the parcellation method, suggested by Nakamura and colleagues (2008), seemed to have added too many insignificant voxels to his analysis as they compared the entire area between olfactory sulcus and the lateral orbital sulcus, while main difference in the study presented in this Chapter was observed in the anterior orbitofrontal cortex between rostral part of the medial orbital sulcus, rostral part of the lateral orbital sulcus and the transverse orbital sulcus. It is also important to notice that the sample recruited for this study was larger than the sample in Nakamura and colleagues (2008). Strikingly, the differences were discovered in the grey matter density amongst ***healthy*** individuals with different orbitofrontal sulcogyral patterns. This suggests that despite the

significant grey matter reduction there are compensatory mechanisms that prevent individuals with the orbitofrontal type III from developing an illness.

These results will be further discussed in **Chapter 8** of this Thesis.

Chapter 7

Brain activation differences associated with the orbitofrontal morphology in healthy population

This chapter reports the brain activation differences that were found in healthy volunteers with various orbitofrontal sulcogyral patterns.

7.1 Introduction

Abnormalities of orbitofrontal cortical folding pattern have previously been reported in patients with schizophrenia (Nakamura, 2007). Those patterns are present before schizophrenia is manifested and are associated with psychotic features (Chakirova *et al.,* 2010) even in the pre-morbid state. The early formation of the orbital sulci and the beginning of formation of cerebral pathways in the 3rd trimester of pregnancy (Chi *et al.,* 1977; Kostovic and Jovanov - Milosevic, 2006) suggests that the shaping of the orbitofrontal sulcogyral patterns might reflect such processes as neuronal migration, local neuronal connection, synaptic development, lamination, formation of cytoarchitecture (Armstrong *et al.,* 1995; Rakic, 1988) and is likely to be exposed to multiple genetic (and possibly environmental) influences (Gurling *et al.,* 2006). In the current study the hypothesis that different OFC sulcogyral patterns will be associated with differences in brain activation and function even within healthy individuals was tested. This hypothesis was assessed using functional Magnetic Resonance Imaging (fMRI) and neuropsychological tests.

7.2 Bipolar Family Study

The information on the Bipolar Family Study is provided in details in **Chapter 5** of this thesis.

7.2.1 Background

The background information on the Bipolar Family Study is provided in details in **Chapter 5** of this thesis.

7.2.2 Demographic and clinical measures

The information on demographic and clinical measures of the participants of the Bipolar Family Study is provided in details in **Chapter 5** of this thesis.

7.2.3 Neuropsychological assessment

The information on neuropsychological assessment of the participants of the Bipolar Family Study is provided in details in **Chapter 5** of this thesis.

7.3 Methods

7.3.1 Participants

The information about participants of the Bipolar Family Study is provided in details in **Chapter 5** of this thesis.

7.3.2 Functional Magnetic Resonance Imaging

See a detailed description of the fMRI methods in **Chapter 2** of this thesis.

7.3.3 Scanning procedure

All participants were scanned at the Scottish Brain Imaging Research Centre on a GE 1.5 Tesla Signa scanner (GE Medical, Milwaukee, Wisconsin). The functional imaging protocol consisted of axial gradient-echo planar images (EPI; repetition time/echo time = 2000/40 msec; matrix = 64 x 64; field of view = 24 cm) acquired continually during the experimental paradigm. Twenty-seven contiguous 5-mm slices were acquired within each repetition time. Each EPI acquisition was run for 404 volumes. The first four volumes were discarded. Visual stimuli were presented using a screen (IFIS, MRI Devices, Waukesha, Wisconsin) placed in the bore of the magnet. The T1 sequence yielded 180 contiguous 1.2-mm coronal slices (matrix = 192 x 192; field of view = 24 cm; flip angle 8°).

Figure 7.1. Example of sentences with different constraint levels.

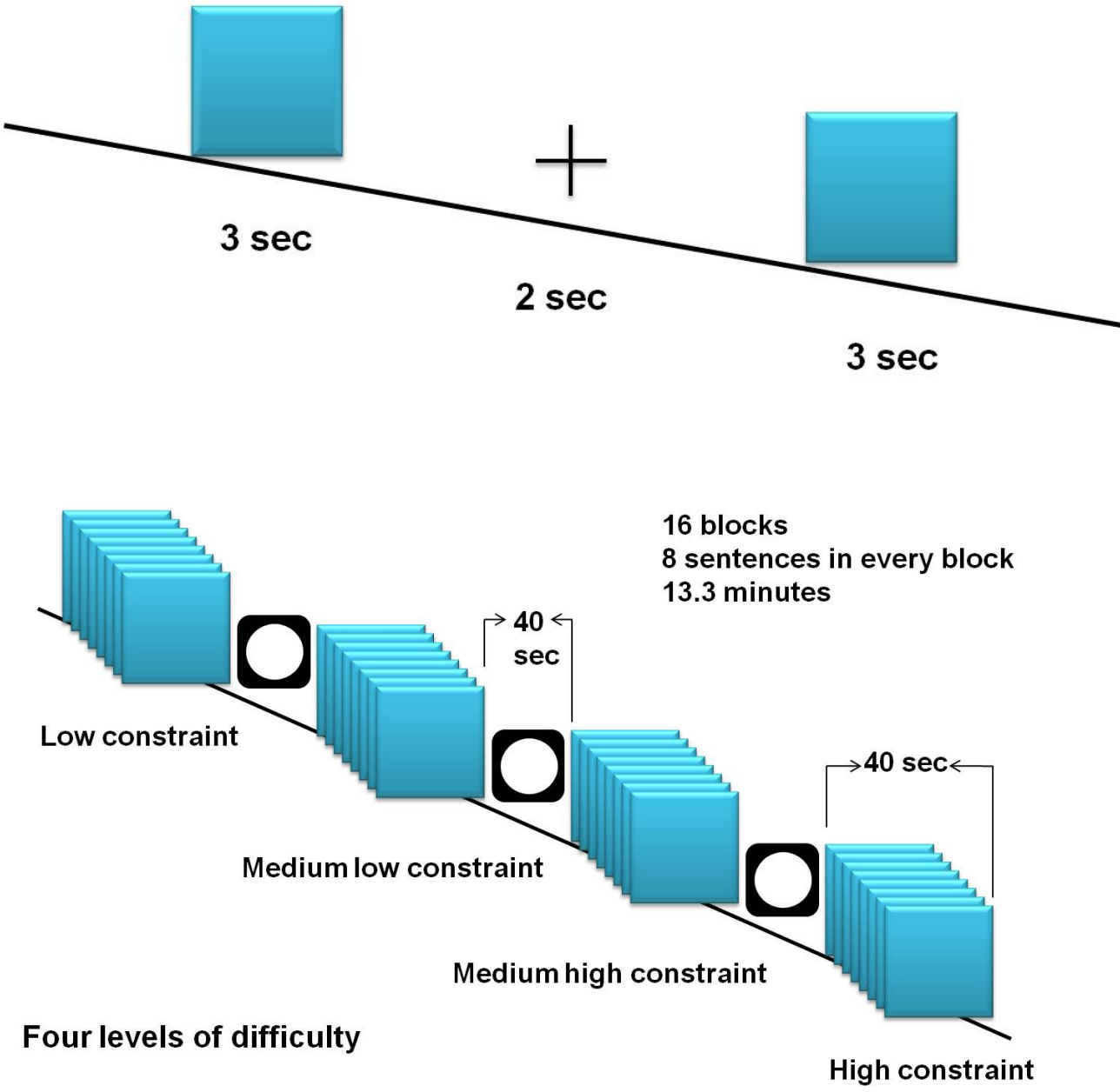
Level of constraint	Example of sentence
Low	The difficult concept was beyond his … His ring fell into a hole in the … Rushing out he forgot to take his … In the distance they heard the…
Medium low	A large stone blocked the entrance to the… Her dress was made of very fine… Diana slowly sank into the hot… They were startled by the sudden …
Medium high	The train was still on … Their picnic was ruined by the … The bad boy was sent to his… When the shooting started they ran for …
High	I could not remember his… At night the old women locked the… He wondered if the storm had done much… Fred realised the old house was up for…

7.3.4 The Hayling Sentence Completion Paradigm (See Figure 7.1 and 7.2)

Participants performed the verbal initiation section of the Hayling Sentence Completion Task while scanned (Whalley *et al.,* 2004). During the experimental procedure a sentence with the last word missing was presented to participants and they were asked to silently think of a suitable word to complete the sentence. When they had done so the participants were required pressing a button to confirm that they were concentrating on the

task. The task had 4 levels of difficulty according to the range of suitable completion words suggested by the sentence constraint: low, medium low, medium high and high (Bloom and Fischler, 1980). Low to high sentence constraint represents decreasing difficulty, the low constraint sentences potentially being completed in many ways (for example, 'His ability to work was…') and the high constraint sentences limited by one possible answer only ('Bob proposed, but she turned him…'). The task also had a baseline visual condition. This design allowed a standard subtraction analysis (all levels of sentence completion difficulty versus baseline) and a parametric analysis examining increasing activation with increasing task constraint. Pseudorandomized block design was used. Each block lasted 40 seconds, consisting of 8 sentences, and each block was repeated four times using different sentences.

Figure 7.2. The Hayling Sentence Completion Paradigm design. The blue quadrants represent blocks with eight sentences in each one of them. For detailed description of the task please see section **7.2.3** of this Chapter.



7.3.5 Image Processing and Analysis

Firstly, DICOM convert functions were used to reconstruct the EPI and T1 images into NIFTI format (Mayo Clinic, Rochester, Minnesota). These functions were available in SPM5 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm/) running in Matlab (MathWorks, Natick, Massachusetts). Secondly, EPI images were realigned to the mean functional image to correct for movement throughout the period of acquisition. The structural (source) and functional (reference) images were coregistered. The anatomic image was segmented. From the previous step the spatial normalization parameters were generated and used to normalize at $2mm^3$ the realigned functional EPI data. Finally, the realigned normalized images were smoothed using an 8 X 8 X 8 mm full width half maximum (FWHM) Gaussian filter.

7.3.6 First-Level Analysis

Statistical Parametric Mapping, version 5 (SPM5) (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm/) was used to perform the general linear model approach. For each individual subject the data was modelled by creating four conditions where each condition was associated with particular level of difficulty (four levels). Each condition was modelled by a boxcar convolved with a synthetic hemodynamic response function. Estimates of the subject's movement were entered as 'covariates of no interest'. The design matrix included a high - pass filter (128 sec). Moreover, serial correlations were accounted for using the autoregressive (Phillips *et al.,* 2003) model. Contrasts were constructed to investigate all four sentence completion conditions versus baseline, as well as areas of increasing activation with increasing task difficulty (the parametric contrast).

7.3.7 Second-Level Analysis

For each contrast of interest, one contrast image per subject was entered into the second-level random effects analyses. In order to examine the potential trait effects, a two-sample *t* - test was conducted to compare the healthy individuals with the orbitofrontal type I, II and III. In order to avoid possible orbitofrontal type *orbitofrontal type interaction (as for this type of comparison group samples were too small) brain activation differences were analysed only in those healthy participants that were identified as having the same orbitofrontal pattern in the left and right hemispheres. Therefore, three groups were composed and examined: those with the orbitofrontal type I in the right and the left hemispheres, with type II in the right and the left hemispheres, and with type III in the right and in the left hemispheres (or those with symmetric scans; see **Chapter 1** and **Chapter 3** for details). The following groups were compared: Type I versus Type II, Type I versus Type III and Type II versus Type III for sentence completion versus baseline and parametric contrasts. All comparisons were covariated for gender, NART IQ, and handedness. The Type I group consisted of 28 images, the Type II group included 9 images, and the Type III group consisted of 4 images.

Statistical maps were thresholded at the standard level of $p = 0.001$ uncorrected, and regions were considered significant at $p = 0.05$ cluster level corrected for multiple comparisons across the whole brain and for region of interest that consisted of frontal lobe (small volume correction). All *p* values quoted are at the cluster level corrected for multiple comparisons. Only clusters larger than 50 voxels were included. Coordinates are reported in Montreal Neurological Institute convention. All images are overlaid onto standard brain in Montreal Neurological Institute space using Mango software package (http://ric.uthscsa.edu/mango).

On the basis of our interest to comparison of the orbitofrontal sulcogyral patterns, small volume correction (SVC) was used for the frontal lobe only. Initially, a whole-brain analysis was conducted as described earlier, and then the small volume correction was applied. The frontal cortex SVC was created using the Wake Forest University PickAtlas (Tzourio-Mazoyer *et al.,* 2002; Maldjian *et al.,* 2003). To account for inter-subject differences, the latter was dilated by two voxels, determined qualitatively using the check-registration function in SPM to a selection of T1 structural images from the current cohort.

7.3.8 Classification of orbitofrontal sulcogyral patterns

The classification of orbitofrontal sulcogyral patterns was described in **Chapters 1** and **3** of this thesis. Additionally, the protocol of identification of the orbitofrontal sulcogyral patterns attached as an **Appendix 1**.

7.3.9 Clinical and neuropsychological assessment

See detailed description of clinical and neuropsychological assessments in the Bipolar Family Study in **Chapter 5**.

7.4 Results

7.4.1 Demographics

See the results section 5.4.1 in **Chapter 5**.

7.4.2 Distribution of the orbitofrontal patterns

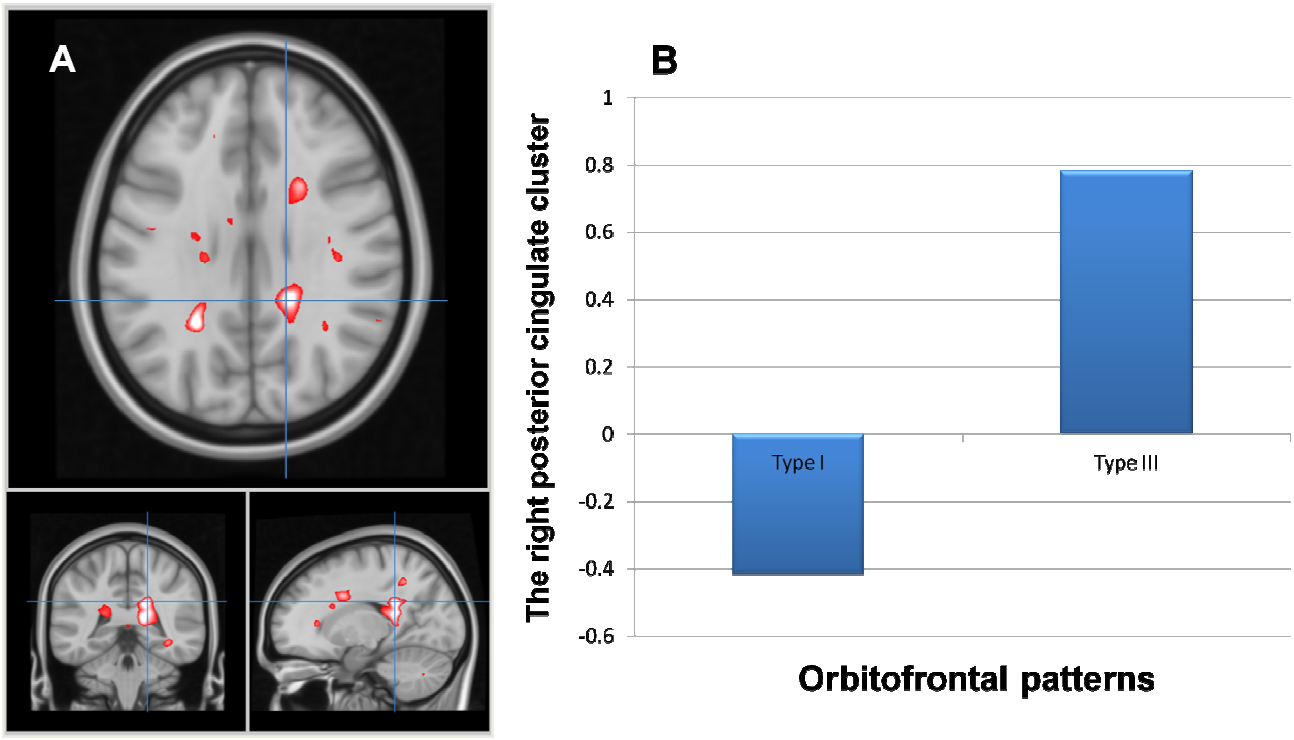
See the results section 5.4.2 in **Chapter 5**.

7.4.3 Activation differences associated with orbitofrontal patterns in healthy controls

Type I versus Type III

The healthy participants with the orbitofrontal type III showed significantly higher activation in the cluster that included the following areas: the right posterior cingulate gyrus (BA 31), right caudate tail, and right extra-nuclear (MNI coordinates of the maximum voxel: x = 18, y = -40, z = 28; T = 4.59, Z = 3.91, K voxel = 215, p corrected non-stationary = 0.009) compared to those controls with the orbitofrontal type I in both hemispheres during the whole brain comparison for the sentence versus baseline contrast (See **Figure 7.3**).

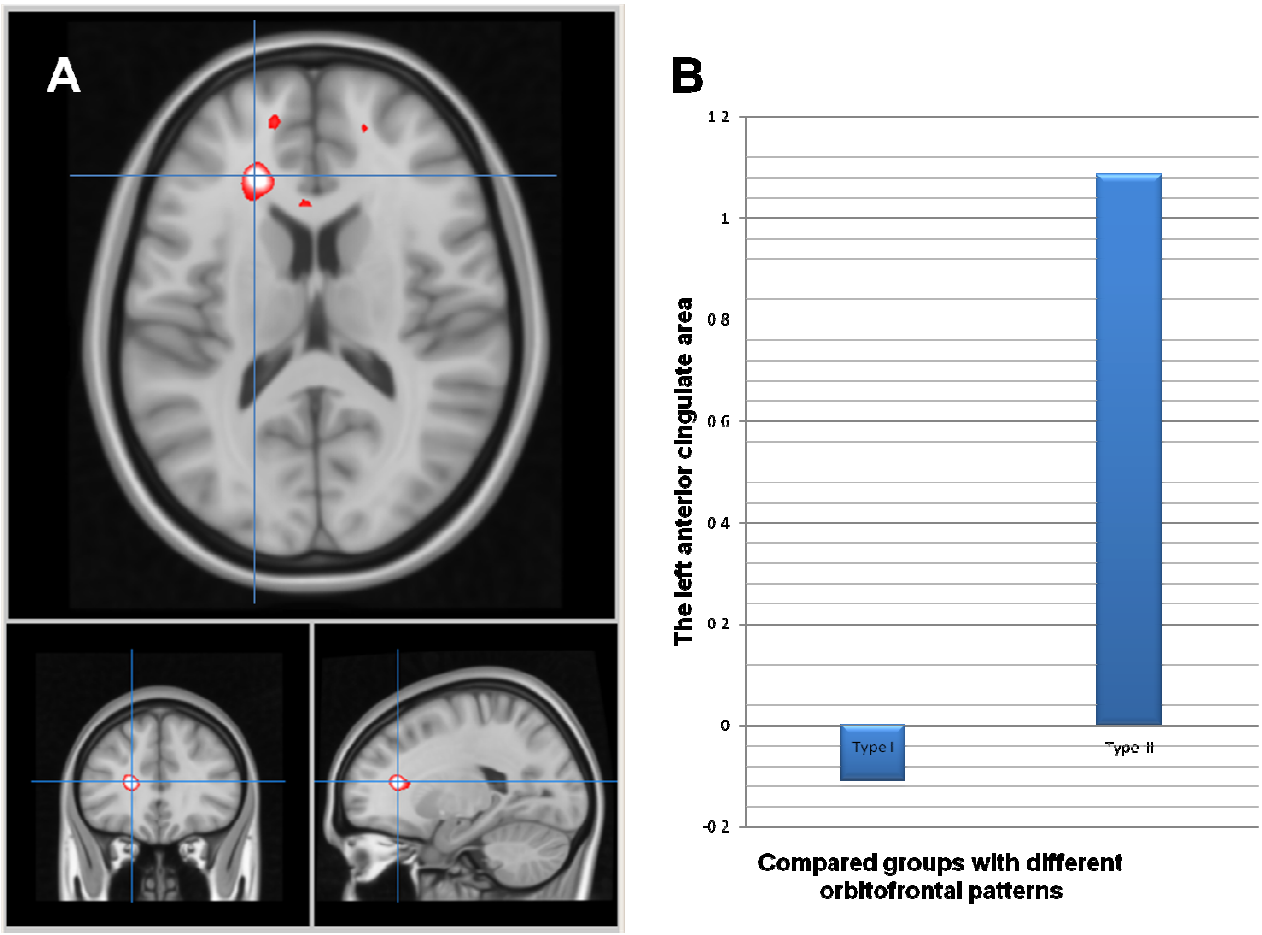
Figure 7.3. Activation contrast between healthy participants with the orbitofrontal type I and healthy individuals with the orbitofrontal risk-type III for sentence completion versus baseline contrast. **(A)** The localization of the cross is pointed at the maximum voxel x = 18, y = -40, z = 28 in the right posterior cingulate area where participants with risk-type III showed greater activation compared to the individuals with the orbitofrontal type I. Cluster is significant at $p < 0.05$. **(B)** Graph demonstrates extracted values from Statistical Parametric Mapping for the right posterior cingulate area (type I versus type III). See text for further details.



The small volume correction for the frontal area revealed another cluster in the left anterior cingulate area (BA 32) where those healthy participants with type III demonstrated greater activation compared to those healthy individuals with type I for parametric contrast (MNI coordinates of the maximum voxel: x = -20, y = 32,

z = 14; T = 6.37, Z = 4.93, K voxel = 122, p corrected non-stationary = 0.008) (See **Figure 7.4**).

Figure 7.4. Activation contrast between healthy participants with the orbitofrontal type I and healthy individuals with the orbitofrontal risk-type III for the parametric contrast. **(A)** The localization of the cross is pointed at the left anterior cingulate area (x = -20, y = 32, z = 14) where participants with the orbitofrontal type III showed greater activation compared to the individuals with the orbitofrontal type I. Cluster is significant at $p < 0.05$. **(B)** Graph demonstrates extracted values from Statistical Parametric Mapping for the left anterior cingulate area. See text for further details.



There was not any significant difference found for comparison type I > type III in either parametric or sentence completion versus baseline contrast.

Type I versus Type II

There was no difference found between these two types either for parametric, nor for sentence completion versus baseline contrast.

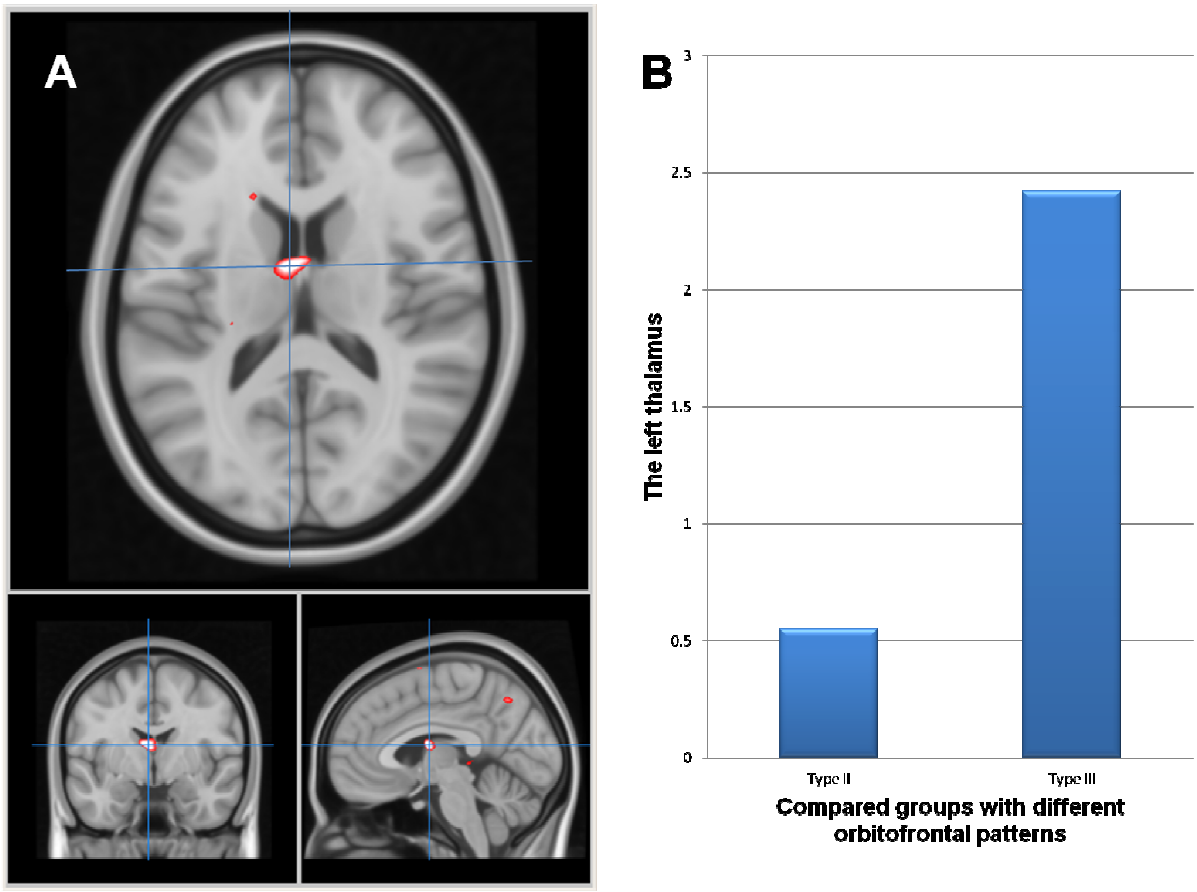
Type II versus Type III

There was not any significant difference found for comparison type II > type III in either parametric or sentence completion versus baseline contrast.

The healthy participants with the orbitofrontal type III in the left and right hemispheres showed significantly higher activation in the following areas for the sentence completion versus baseline contrast:

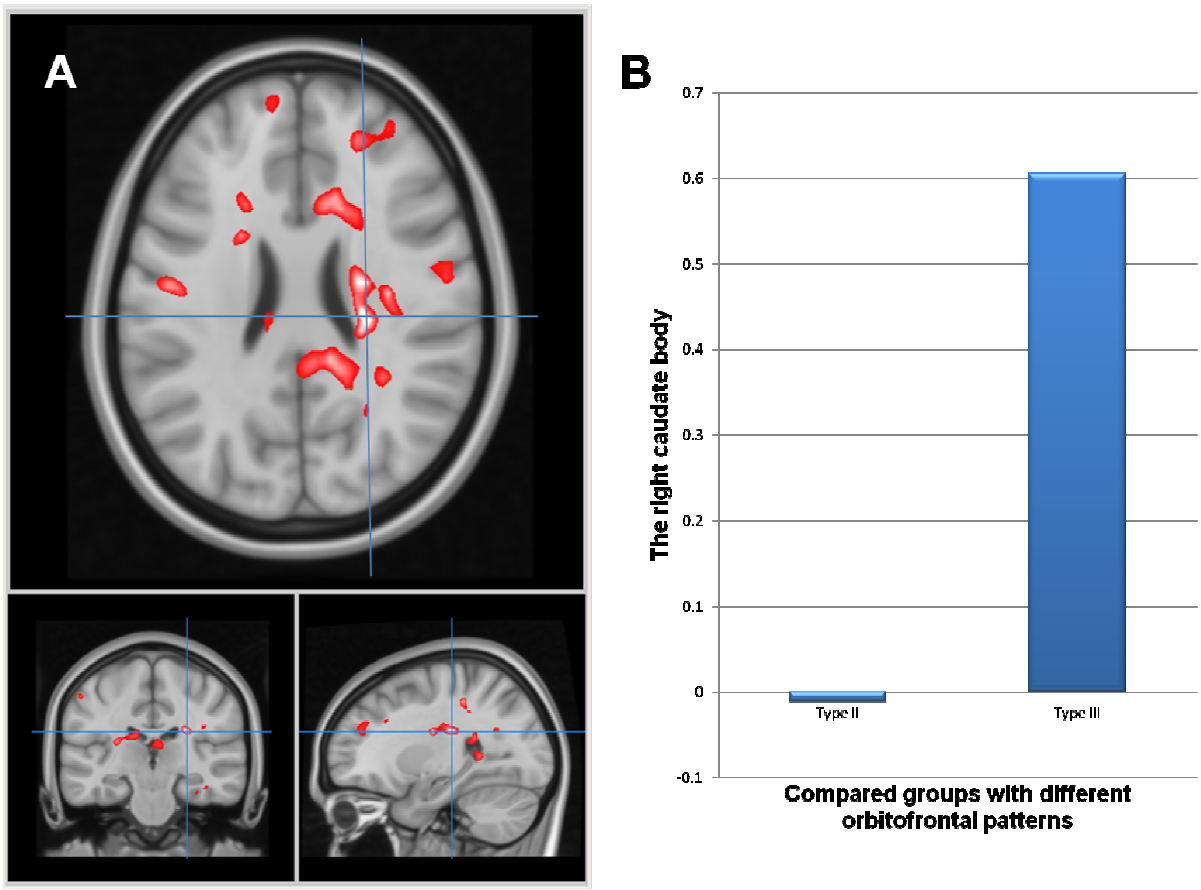
1. The left thalamus, left caudate body, left anterior nucleus (MNI coordinates: x = - 4, y = - 4, z = 14; T = 9.36, Z = 4.52, K voxel = 117, p corrected non-stationary = 0.016; See **Figure 7.5**);

Figure 7.5. Activation contrast between healthy participants with the orbitofrontal type II and healthy individuals with the orbitofrontal risk - type III for the sentence completion versus baseline contrast. **(A)** The localization of the cross is pointed at the left thalamus (x = - 4, y = - 4, z = 14) where participants with the orbitofrontal type III showed greater activation compared to the individuals with the orbitofrontal type II. Cluster is significant at $p < 0.05$. **(B)** Graph demonstrates extracted values from Statistical Parametric Mapping for the left thalamus. See text for further details.



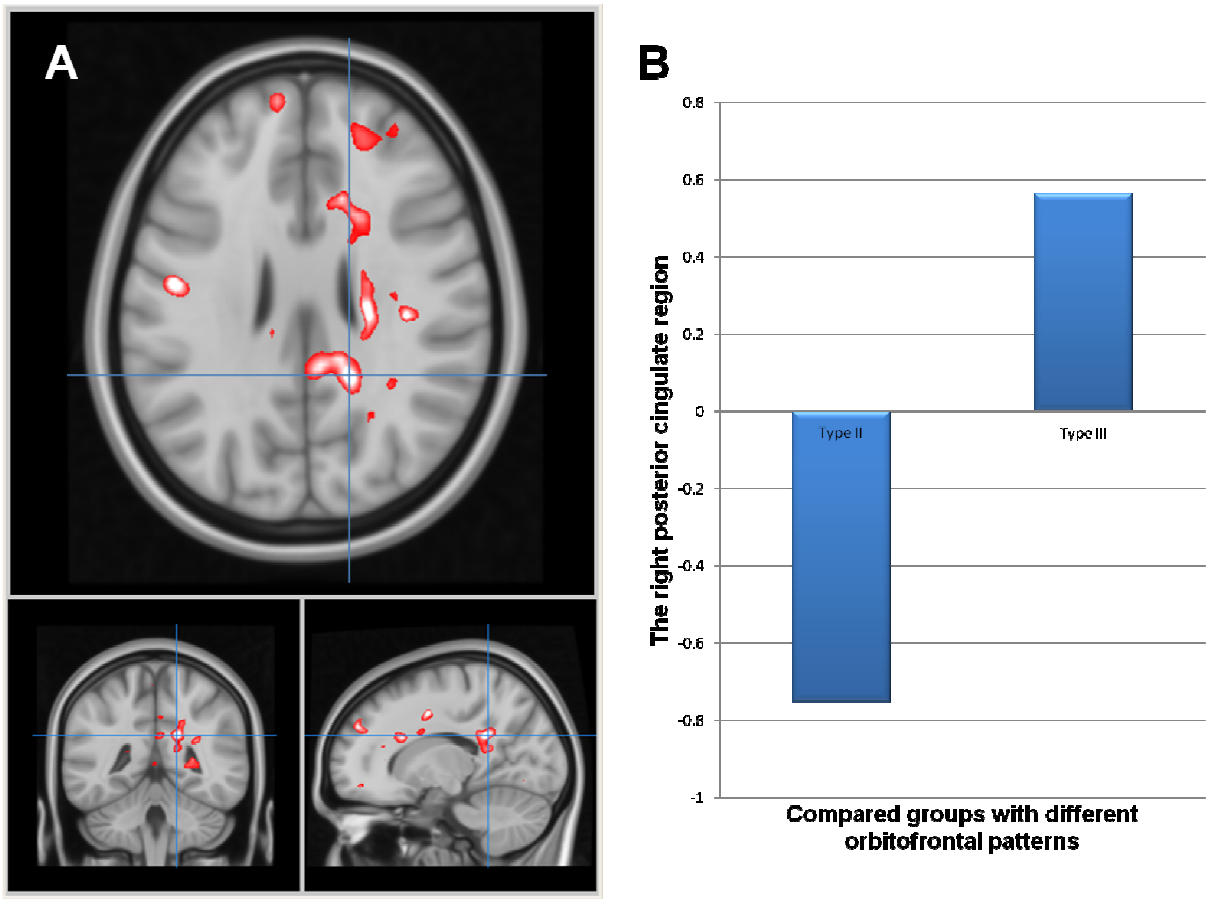
2. The right caudate tail and body and the right insula (BA 13) (MNI coordinates: x = 26, y = -24, z = 24; T = 9.14, Z = 4.48, K voxel = 81, p corrected non-stationary = 0.001; See **Figure 7.6**);

Figure 7.6. Activation contrast between healthy participants with the orbitofrontal type II and healthy individuals with the orbitofrontal risk - type III for the sentence completion versus baseline contrast. **(A)** The localization of the cross is pointed at the right caudate body (x = 26, y = - 24, z = 24) where participants with the orbitofrontal type III showed greater activation compared to the individuals with the orbitofrontal type II. This cluster is significant at $p < 0.05$. **(B)** Graph demonstrates extracted values from Statistical Parametric Mapping for the right caudate body. See text for further details.



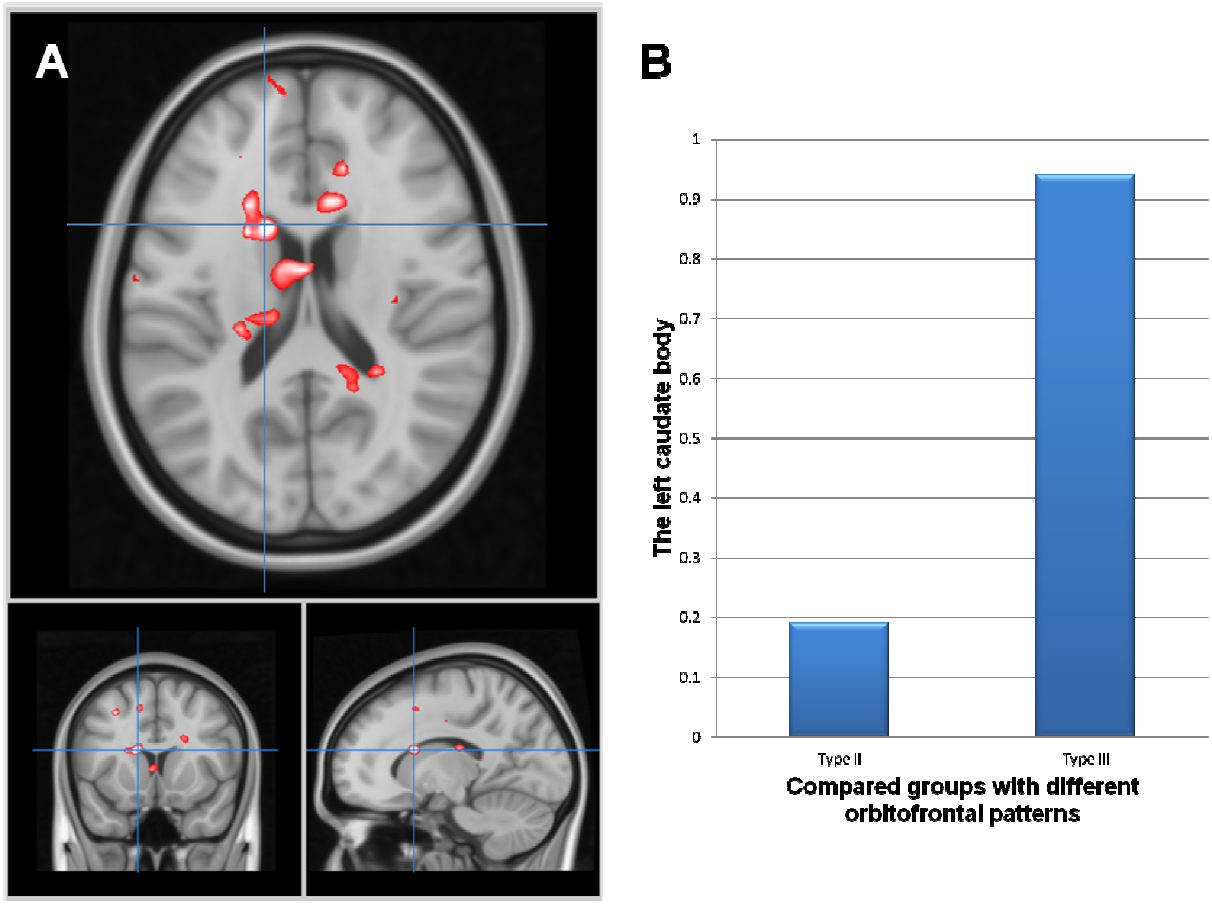
3. The right posterior cingulate gyrus (BA 23, 31), right precuneus (BA 31) and right extra-nuclear (MNI coordinates: x = 16, y = - 44, z = 26; T = 7.02, Z = 4.00, K voxel = 113, p corrected non-stationary = 0.025; See **Figure 7.7**);

Figure 7.7. Activation contrast between healthy participants with the orbitofrontal type II and healthy individuals with the orbitofrontal risk - type III for the sentence completion versus baseline contrast. **(A)** The localization of the cross is pointed at the right posterior cingulate region (x = 16, y = - 44, z = 26) where participants with the orbitofrontal type III showed greater activation compared to the individuals with the orbitofrontal type II. This cluster is significant at $p < 0.05$. **(B)** Graph demonstrates extracted values from Statistical Parametric Mapping for the right posterior cingulate area. See text for further details.



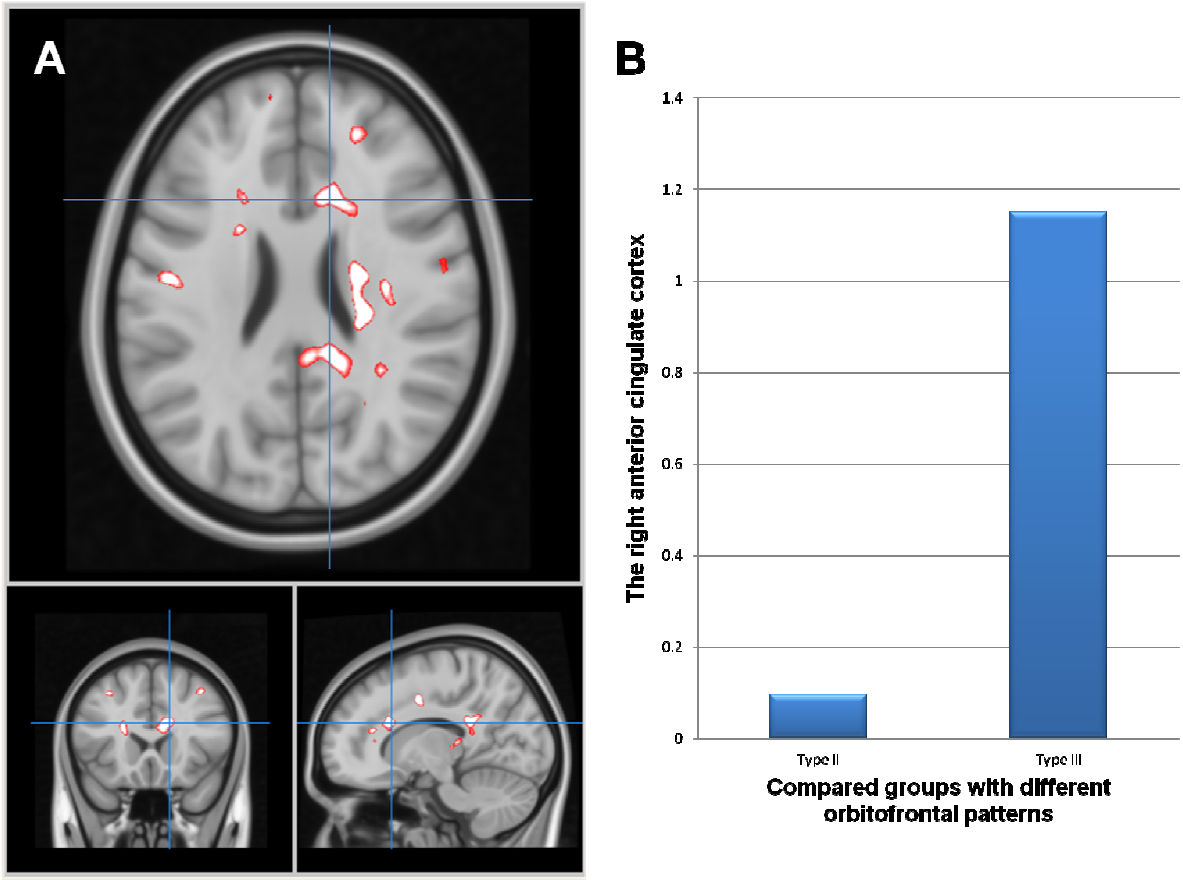
4. The left caudate body, left lentiform nucleus, putamen and left cingulate gyrus (BA 32) (MNI coordinates: x = - 14, y = 12, z = 18; T = 6.83, Z = 3.95, K voxel = 80, p corrected non-stationary = 0.010; See **Figure 7.8**);

Figure 7.8. Activation contrast between healthy participants with the orbitofrontal type II and healthy individuals with the orbitofrontal risk - type III for the sentence completion versus baseline contrast. **(A)** The localization of the cross is pointed at the left caudate body (x = - 14, y = 12, z = 18) where participants with the orbitofrontal type III showed greater activation compared to the individuals with the orbitofrontal type II. This cluster is significant at $p < 0.05$. **(B)** Graph demonstrates extracted values from Statistical Parametric Mapping for the left caudate body. See text for further details.



5. The right anterior cingulate cortex and cingulate gyrus (BA 24, 32) and right caudate body (MNI coordinates: x = 14, y = 20, z = 24; T = 5.83, Z = 3.66, K voxel = 81, p corrected non-stationary = 0.032), when they were compared to those healthy individuals with the orbitofrontal type II in both hemispheres during the whole brain comparison for the sentence completion versus baseline contrast (See **Figure 7.9**).

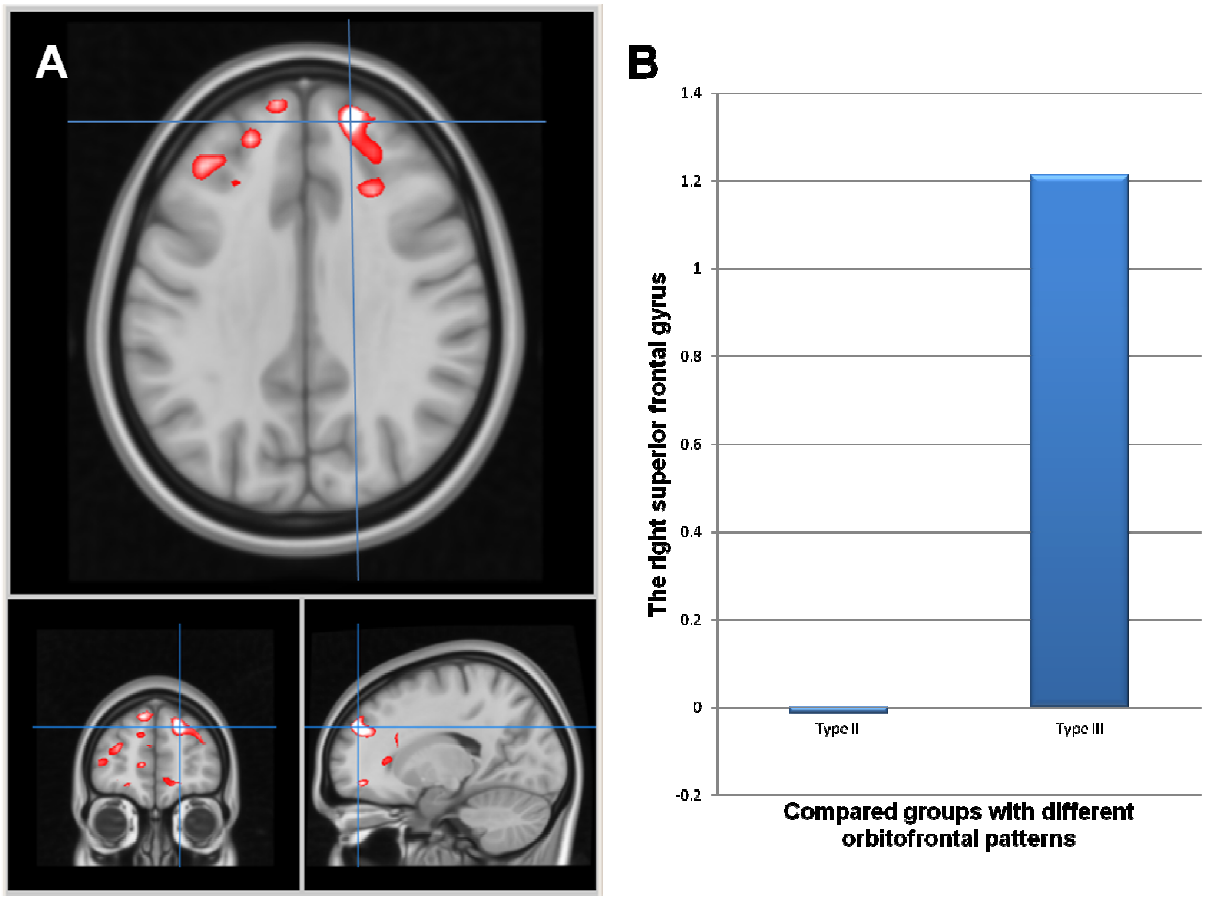
Figure 7.9. Activation contrast between healthy participants with the orbitofrontal type II and healthy individuals with the orbitofrontal risk-type III for the sentence completion versus baseline contrast. **(A)** The localization of the cross is pointed at the right anterior cingulate cortex (x = 14, y = 20, z = 24) where participants with the orbitofrontal type III showed greater activation compared to the individuals with the orbitofrontal type II. This cluster is significant at $p < 0.05$. **(B)** Graph demonstrates extracted values from Statistical Parametric Mapping for the right anterior cingulate cortex. See text for further details.



Additional small volume correction analysis to the frontal area revealed one more cluster localised in the right superior frontal gyrus (BA 8, 9) and middle

frontal gyrus (BA 8, 9) (MNI coordinates: x = 18, y = 52, z = 32; T = 7.16, Z = 4.04, K voxel = 57, p corrected non - stationary = 0.006) when the participants possessing the orbitofrontal type III demonstrated increased activation in this area compared to healthy volunteers with type II for sentence completion versus baseline contrast (See **Figure 7.10**).

Figure 7.10. Activation contrast between healthy participants with the orbitofrontal type II and healthy individuals with the orbitofrontal risk - type III for the sentence completion versus baseline contrast. **(A)** The localization of the cross is pointed at the right superior frontal gyrus (x = 18, y = 52, z = 32) where participants with the orbitofrontal type III showed greater activation compared to the individuals with the orbitofrontal type II. This cluster is significant at $p < 0.05$. **(B)** Graph demonstrates extracted values from Statistical Parametric Mapping for the right superior frontal gyrus. See text for further details.



7.5 Discussion

Brain activation differences were analysed using fMRI technique in those healthy individuals who had the same orbitofrontal pattern in both the right and the left hemispheres (symmetric scans; See **Chapters 1** and **3** for details).

Functional MRI revealed increased activation in healthy individuals with the orbitofrontal type III compared to those healthy volunteers with the orbitofrontal type I in the following areas: the right posterior cingulate gyrus (BA 31), right caudate tail for the sentence completion versus baseline contrast and in the left anterior cingulate (BA 32) area for the parametric contrast. These results are particularly interesting knowing that both cingulate cortex and caudate nucleus are connected to the orbitofrontal region. Further, association of the paracingulate and orbitofrontal cortices risk variants increases their predictive value for schizophrenia and bipolar affective disorder (See **Chapters 3**, **4** and **5**). Moreover, there was a decrease of grey matter density found in the BA 32 region for the same comparison using the VBM method (Type III versus Type I; See **Chapter 6** for details). Furthermore, Brodmann Area 32 is the dorsal part of the anterior cingulate and most commonly active during the Stroop task (See **Chapter 4** for details).

This result demonstrates that even within healthy controls those with type III differ from those healthy participants with the orbitofrontal type I. This suggests that the orbitofrontal pattern III represents the grey matter and BOLD signal abnormalities, probably due to genes, and neurodevelopmental and environmental influences. Given these results individuals with the orbitofrontal type III in both left and right hemispheres seemed to be 'less healthy' even if they are within controls when compared to those with the

orbitofrontal type I. This suggests the orbitofrontal type III to be a marker of neurodevelopmental problems.

Unlike with structural MRI analysis, functional MRI did not reveal any brain activation difference between healthy individuals with the orbitofrontal type I and II in both hemispheres. The possible explanation is the limitations of the fMRI method with regards to examining the orbitofrontal region including areas BA 11 and BA 47 due to the large susceptibility artefacts.

Similarities between healthy individuals with the orbitofrontal types I and II by fMRI analysis was particularly important as it might explain to some extend differences between healthy individuals with the orbitofrontal types II and III. Interestingly, there were more areas of activation differences between type II and III individuals then between type I and III individuals. These areas included the left thalamus, left anterior nucleus, right caudate tail, the right and left caudate body, right insula (BA 13), right posterior cingulate gyrus (BA 23, 31), right precuneus (BA 31), left lentiform nucleus, putamen, left cingulate gyrus (BA 32), right anterior cingulate gyrus (BA 24, 32), the right superior frontal gyrus (BA 8, 9) and middle frontal gyrus (BA 8. 9) for the sentence versus baseline contrast.

The cingulate region is a particularly important finding for this study given that an association between paracingulate and orbitofrontal morphology improves negative predictive value and allows excluding those high risk individuals that have better chances to remain well with 92-96% of accuracy.

These results will be further discussed in **Chapter 8** of this Thesis.

Chapter 8

The theory of predictive associations of the orbitofrontal sulcogyral patterns

This chapter is a description and a partial justification of a theory that is based on orbitofrontal morphological sulcogyral patterns. All the research work that was summarized in the previous chapters of this thesis has led to understanding that there is a system to the orbitofrontal types and their structural and functional associations. This system is based on the orbitofrontal cytoarchitectonic structure, includes the association of the orbitofrontal patterns with the paracingulate sulcus, and has become a foundation for the theory of predictive associations.

8.1 Introduction to the theory of predictive associations of the orbitofrontal sulcogyral patterns

The main purpose of this study was to investigate the orbitofrontal morphology in a range of the cohorts, different diagnostic groups and healthy individuals, to establish whether the orbitofrontal sulcogyral patterns are associated with mental illnesses and represent structural and functional abnormalities within the brain, and to examine whether the orbitofrontal patterns on their own or in combination with the anterior cingulate morphology predict development of schizophrenia or bipolar affective disorder. This could be important for medical practice and for human brain research as it could give a valuable tool to predict and potentially to prevent those mental illnesses.

8.1.1 The importance of the orbitofrontal cortex

The orbitofrontal cortex has been reported as an important part of executive functioning, motivation, decision - making and goal - directed behaviour (Walton *et al.,* 2004). This region also plays a role in the processing of emotions including hedonic experience (Ongur and Price, 2000; Kringelbach, 2005). Given that the orbitofrontal cortex is a large and multifunctional part of the human cortex that is widely connected to many other regions of the brain, it became a specific region of interest of this study.

The orbitofrontal cortex is connected to many brain areas including cingulate cortex (Van Hoesen *et al.,* 1993), insula (Mesulam and Mufson, 1982), and thalamus (Ongur and Price, 2000). The orbitofrontal cortex is innervated by cholinergic and aminergic subcortical fibres (Morecraft *et al.,* 1992). The pathway between the orbitofrontal cortex and striatum may control dopaminergic substantia nigra pars compacta neurons and, therefore, influence the goal - directed behaviour Rolls (1999 a). Strikingly, the

cholinergic connections between the orbitofrontal cortex and the nucleus basalis of Meynert might allow the orbitofrontal cortex to control the cholinergic inputs to the entire cerebral cortex. Such an influential network suggests that the orbitofrontal cortex is an important brain area in a search for the structural feature that may predict the development of psychiatric illnesses.

Numerous neurotransmitter systems modulate neurotransmission within the orbitofrontal cortex including serotonergic (Way *et al.,* 2007; Rosell *et al.,* 2010), dopaminergic (Moghaddam, 2002; Calaminus and Hauber, 2008; De Almeida and Mengod, 2010; Lodge, 2011), noradrenergic (Jodo *et al.,* 1998), cholinergic (Roberts *et al.,* 1992; Everitt and Robbins, 1997; Himmelheber *et al.,* 2001; Hasselmo and Sarter, 2011), glutamatergic (Moghaddam, 2002; Miguel-Hidalgo *et al.,* 2010), GABAergic (De Almeida and Mengod, 2010), norepinephrinergic (Young *et al.,*1994), glucocorticoid and peptidergic (corticotrophin - releasing factor function) (Carrol et al., 1981; Young et al., 1993; Catapano and Manji, 2007). The monoamine neurotransmitter systems have been of particular interest as a primary target of most antidepressant drugs while the dopaminergic receptors were the main priority of the antipsychotics. This means that two major psychiatric illnesses - schizophrenia and bipolar affective disorder, whose neurodevelopment is associated with the dysfunction of particular neurotransmitter systems, might be related to the structural and functional abnormalities in the orbitofrontal regions. Particularly, bipolar affective disorder was related to the serotoninergic system abnormalities in the orbitomedial cortex and could be treated with the selective serotonin reuptake inhibitors (Saxena and Rauch, 2000; Drevets, 2001; Lucey, 2001), while schizophrenia was associated with the elevated level of dopamine.

A number of studies (See **Chapter 2** for details) reported brain structure abnormalities in patients with bipolar affective disorder and schizophrenia

(Johnstone *et al.,* 2005; Owens and Johnstone, 2006; Gruber *et al.,* 2008; McIntosh *et al.,* 2008). Moreover, evidence suggests that acquired damages in the left prefrontal cortex may result in negative symptoms of schizophrenia and in stabilized mood (Pang and Lewis, 1996; See **Chapter 1** for details). Furthermore, Curtis and colleagues (2001) reported a different pattern of frontal responses in patients with bipolar disorder compared to those with schizophrenia. Considering that the orbitofrontal cortex has such extensive influence through its connections and neurotransmitter systems and is known to be important in emotional processing and executive functioning (Ongur and Price, 2000; Kringelbach, 2005; Walton *et al.,* 2004), it seems reasonable to suggest the involvement of this region in pathophysiology and symptoms of bipolar affective disorder and schizophrenia. Comparing symptomatology of the two major psychiatric illnesses such as social withdrawal, the insidious onset of schizophrenia *versus* more socially appropriate premorbid behaviour and the rapid onset of bipolar disorder (Cannon *et al.,* 1997; Kutcher *et al.,* 1998), and differences in pathogenic theories of the two disorders (association with dysfunction of dopamine and glutamate neurotransmitter systems in the development of schizophrenia compared to the involvement of serotonin and norepinephrine neurotransmitter systems in bipolar disorder), it might be possible to suggest the OFC as an area with significant potential for distinguishing the two disorders.

8.1.2 Schizophrenia and bipolar disorder

The orbitofrontal cortex was examined in groups with two major mental illnesses: schizophrenia and bipolar affective disorder. Schizophrenia is characterized by positive and negative symptoms including impairment in the perception or expression of reality that is manifesting as hallucinations, delusions, disorganized speech and thinking and significant occupational or social dysfunction (See **Chapter 2** for details). The positive symptoms are

used to describe behavioural and perceptional excesses and include delusions, hallucinations, disorganised speech and behavioural abnormalities. The negative symptoms symbolize loss of normal function (Strauss *et al.,* 1974) and consist of alogia, avolition, affective blunting, and anhedonia.

Bipolar affective disorder is well known as a highly heritable psychiatric illness that is characterised by unstable mood and disrupted behaviour and could develop either manic or depressive episodes interspersed with periods of remission. During manic or hypomanic (less severe manic) episodes, patient experiences decreased sleep, increased drive and grandiose affect. If untreated it might culminate in psychosis.

8.1.3 The theory of predictive associations of the orbitofrontal sulcogyral patterns

The theory of predictive associations of the orbitofrontal sulcogyral patterns is an outcome of analysing the orbitofrontal sulcogyral patterns and their associations in three independent studies: the Edinburgh High Risk Study (See **Chapter 4** for details), the Bipolar Family Study (See **Chapter 5, 6** and **7** for details), and the study that includes patients with schizophrenia, bipolar disorder and their unaffected relatives (the Psychosis Study; See **Chapter 3** for details).

The theory of predictive associations of the orbitofrontal sulcogyral patterns suggests the following:

1. Orbital sulci form four sulcogyral patterns. The orbitofrontal sulcogyral patterns are distributed unequally but with more or less constant proportion in healthy population. Their distribution might be altered in patients with mental illnesses. This alteration could differ and depend on a particular illness.

2. The presence or absence of additional orbital sulci (posterior, intermediate orbital sulci or sulcus fragmentosus) might affect some of characteristics of the orbitofrontal sulcogyral patterns.

3. The orbitofrontal sulcogyral patterns and the paracingulate sulcus could share similar gender effects: males in the right hemisphere for both orbitofrontal and paracingulate morphology and females in the left hemisphere for both orbitofrontal and paracingulate morphology. This suggests that a gender effect could play a role in a prediction of mental illnesses and be a part of the predictive system of markers.

4. Such structural features like possession of the symmetric orbitofrontal pattern distribution within the brain, continuity of the orbital and cingulate sulci, and an appearance of the prominent paracingulate sulcus variant in the individuals at high risk of developing schizophrenia or bipolar disorder might have a protective role.

5. Each orbitofrontal pattern might be associated with certain brain functional and structural characteristics. These associations include structural brain alterations, changes in brain activation, connectivity, personality traits and altered cognitive functions that could be evident even in healthy controls. The associations of similar orbitofrontal sulcogyral patterns in the right and in the left hemispheres could vary between each other (the orbitofrontal type III in the left hemisphere may have associations different from those of the orbitofrontal type III in the right hemisphere).

6. The orbitofrontal sulcogyral patterns might change some of their characteristics in diagnostic groups (patients with schizophrenia and bipolar disorder and their unaffected relatives, and in those at high risk of developing schizophrenia and bipolar disorder) compared to healthy individuals.

7. Orbitofrontal patterns could be associated and/or connected to the paracingulate and cingulate sulcus. The right orbitofrontal cortex might be connected to the left orbitofrontal cortex and *vice versa*. The right orbitofrontal cortex could be associated not only to the right ACC but also to the left anterior cingulate area. Likewise, the left orbitofrontal cortex might be associated not only to the left ACC, but also to the right anterior cingulate area.

8. There could be an interaction between the orbitofrontal sulcogyral patterns located in the right and in the left hemisphere within one brain. This might be correct even for the symmetric orbitofrontal cortex. In the symmetric brain two identically rated orbitofrontal patterns could potentially reduce an effect of each other's presence. In this sense, it would be safer to have the symmetric brain with the orbitofrontal type III in the right and in the left hemisphere than to have an asymmetric brain with type III in the one of the hemispheres only.

9. The connection between the orbitofrontal and cingulate morphology might allow a combination of these patterns into new system that could predict the development of mental illnesses including schizophrenia and bipolar affective disorder. In this system several patterns might be united and a predictive value could be defined as a value of a whole system (the combination of the patterns) rather than a predictive value of one pattern separately. In this system the orbitofrontal sulcogyral patterns might have a senior position towards the paracingulate sulcus as unlike the paracingulate sulcus the lateral and medial orbital sulci are always present. This predictive system might include an effect of the specific genes, gender, features associated with the intermediate orbital sulcus and posterior orbital sulcus.

10. The orbitofrontal sulcogyral patterns could be associated with genes including dysbindin and DISC1.

8.2 Discussion of the theory of predictive associations of the orbitofrontal sulcogyral patterns

Every statement of this theory is an outcome of the orbitofrontal morphology analyses described in the previous chapters of this thesis and/or literature review. It is, therefore, supported by the data described in this thesis or at least by the previous publications. The following are the discussion of the main statements of the theory of predictive associations of the orbitofrontal sulcogyral patterns and the supporting findings.

8.2.1 Orbital sulci form four sulcogyral patterns. The orbitofrontal sulcogyral patterns are distributed unequally but with more or less constant proportion in healthy population. Their distribution might be altered in patients with mental illnesses. This alteration could differ and depend on a particular illness.

There are three main orbital sulci that were identified in the orbitofrontal surface: lateral orbital sulcus, medial orbital sulcus and transverse orbital sulcus (Chiavaras and Petrides, 2000). They were found to be varying in length and connectivity. The connectivity of the rostral and caudal parts of the lateral and medial orbital sulci through the transverse orbital sulcus became a basis for the classification of the orbitofrontal sulcogyral patterns. Appearance of additional sulci including the intermediate and posterior orbital sulci, and the sulcus fragmentosus increases the variability and complexity of the orbitofrontal sulcogyral structure that complicates an identification of the orbitofrontal sulcogyral patterns.

Despite the known variability of orbitofrontal sylcogyral morphology, Chiavaras and Petrides (2000) developed a classification by which orbitofrontal sulcogyral patterns could be separated into three types (Types I, II and III) based on connectivity of the two main orbital sulci: medial and

lateral orbital sulci through the third one - transverse orbital sulcus, with type II being mostly connected and type III being the mostly disconnected type. The orbitofrontal type I had connected lateral orbital sulcus and disconnected medial orbital sulcus. Chiavaras and Petrides (2000) reported the prevalence of type I in a healthy Canadian population (identified in 56% of hemispheres) with the minority of two other types: type II was seen in 30% of hemispheres while type III only appeared in 14% of hemispheres.

Later Nakamura and colleagues (2007) announced the alteration of orbitofrontal cortical folding patterns in patients with schizophrenia with increased type III and reduced type I in the right hemisphere. The authors also noticed that possession of type III in patients with schizophrenia was associated with poorer socioeconomic status, more severe psychotic symptoms and more severe cognitive impairment when compared with patients of any other orbitofrontal pattern (Nakamura *et al.,* 2007). Chakirova and colleagues (2010) looked at those at genetically high - risk of developing schizophrenia and established that the orbitofrontal patterning is altered even before schizophrenia is manifested. The authors also enhanced Chiavaras' classification with a rear type IV that had the disconnected lateral orbital sulcus and connected medial orbital sulcus.

The described four types were identified in all three analysed cohorts, including the Bipolar Family Study (**Chapter 5**), the Edinburgh High Risk Study (**Chapter 4**), and the Psychosis Study (**Chapter 3**). Although, the orbitofrontal type IV was acknowledged in all three cohorts, it was discovered in each study in small numbers and was excluded from further analysis.

In the study of seven groups patients with schizophrenia had increased presence of the orbitofrontal type III and a reduced frequency of the orbitofrontal type I in the right hemisphere. This finding was somewhat consistent with the results from the Edinburgh High Risk Study where the

expression of the orbitofrontal type III was increased while the orbitofrontal type I expression was reduced in the right hemisphere in patients in their first episode of schizophrenia and in those at high risk of developing schizophrenia who became ill when compared to healthy controls or to those at high risk of developing schizophrenia who remained well.

In the Psychosis Study (See **Chapter 3** for details) patients with bipolar disorder had an increased frequency of the orbitofrontal type III in the right and left hemisphere. The orbitofrontal type I was less frequent in patients with bipolar disorder in the right and left hemisphere as well. This finding was at some extend consistent with the results from the Bipolar Family Study (See **Chapter 5** for details), where those individuals at high risk of developing bipolar disorder who became ill had an increased frequency of the orbitofrontal type III and a reduced frequency of the orbitofrontal type I in the right and left hemispheres.

In the Psychosis Study unaffected relatives of patients with bipolar disorder and schizophrenia did not differ in the distribution of the orbitofrontal patterns from healthy individuals and from each other (See **Chapter 3** for details). Similarly, those at high risk of developing schizophrenia or bipolar disorder who remained well had a distribution of the orbitofrontal patterns similar to those of healthy individuals (See **Chapters 4** and **5** for details). In the EHRS those at high risk who became ill had a distribution of the orbitofrontal patterns similar to the orbitofrontal pattern distribution in individuals at their first episode of schizophrenia. Importantly, patients with schizophrenia and bipolar disorder differed from each other in the distribution of the orbitofrontal ***type III in the left hemisphere*** (See **Chapter 3** for details).

It is important to notice that a family history of mental illnesses might affect the distribution of the orbitofrontal patterns in the left hemisphere in patients with bipolar disorder and a family history of bipolar disorder only, in patients

with bipolar disorder and a family history of both bipolar disorder and schizophrenia, and in patients with schizophrenia. It is notable that the orbitofrontal type III is not as frequent in the left hemisphere in the bipolar patients with a family history of both bipolar disorder and schizophrenia as in other two groups. The distribution of the orbitofrontal type III in the left hemisphere the bipolar disorder from mixed families could be placed in between the distribution of this pattern in patients with schizophrenia and its distribution in the bipolar patients with a family history of bipolar disorder only (See **Figure 3.10** for details).

This data suggests that the orbitofrontal sulcogyral patterns differ in their association with mental illnesses. Although, the orbitofrontal type III could be linked to both schizophrenia and bipolar disorder, there is a hemispherical asymmetry to this association. The orbitofrontal ***type III in the right hemisphere*** might be more connected to schizophrenia, while the orbitofrontal ***type III in the left hemisphere*** could be associated to bipolar disorder. This association between the left type III and bipolar disorder is particularly interesting in the light of a single case study described in **Chapter 1** (See **1.1.1.2 A single case study**, p.4). In this case patient with bipolar disorder and a family history of bipolar disorder 'switched' from being a bipolar patient to having a treatment - resistant schizophrenia after his left prefrontal cortex was damaged and removed. This could be explained by the distribution of the dopaminergic receptors in the orbitofrontal and medial prefrontal cortex that appeared to be significantly higher in the left hemisphere (Slopsema *et al.,* 1982). Given that the removal of the left prefrontal cortex will result in the significant reduction of the number of dopaminergic receptors. This might lead to an increase in the dopamine level and, therefore, in the development of schizophrenic-like symptoms. Furthermore, considering that antipsychotic medication must interact with the dopaminergic receptors in order to reduce psychotic symptoms, absence of those receptors might results in treatment-resistant schizophrenia.

Further, it was important to examine whether the orbitofrontal type II could be associated with any mental illness. The preliminary examination of the orbitofrontal patterns distribution in individuals with autism suggested that this particular pattern could reflect brain structural and functional abnormalities associated with the autism – spectrum disorder.

There is considerable evidence that the orbitofrontal cortex plays a role in the pathophysiology of autism (Dawson, 2002; Salmond, 2003; Bachevalier, 2006), abnormalities of the structure likely being particularly important in the impaired social interactions so characteristic of the condition. Specifically, the right lateral subdivision is believed to be important in social cognition (O'Doherty, 2001; Vollm, 2006), and decreased grey matter volume has been reported in children with autism associated with social deficits (Girgis, 2007). Abnormal orbitofrontal connectivity has also been observed in autism, being reported in fronto - striatal, fronto – parietal pathways and the orbitofrontal – amygdala circuit (Bachevalier, 2006; Silk, 2006; Just, 2007). Abnormalities of orbitofrontal cortical folding pattern have previously been reported in patients with schizophrenia (Nakamura *et al.,* 2007). The purpose of this study was to investigate whether such abnormalities were also present in people with autism spectrum disorder.

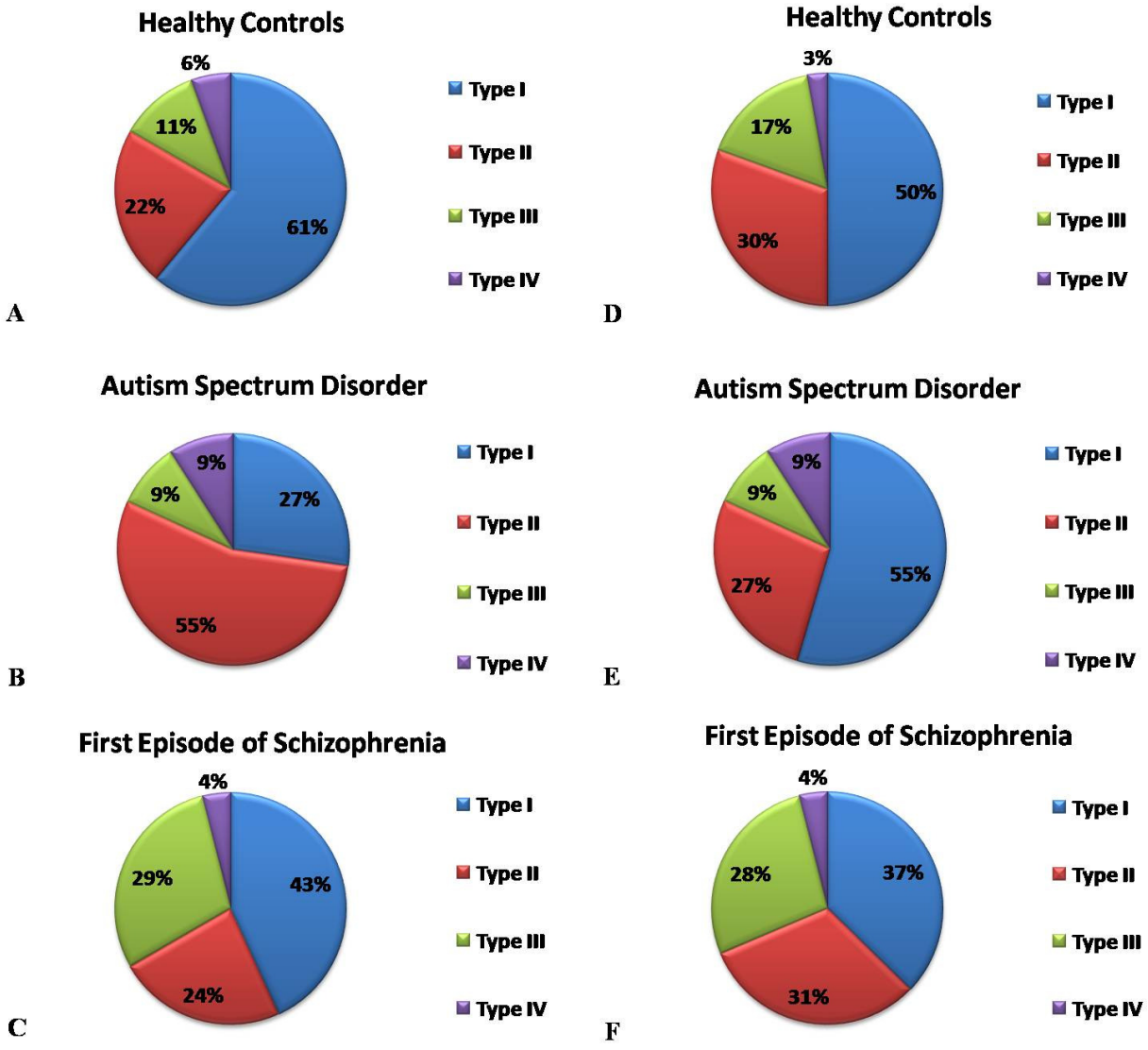
Eleven participants with autism spectrum disorder, thirty four patients in their first episode of schizophrenia and thirty six control subjects had a structural Magnetic Resonance Imaging scan of the brain. Based on connectivity of three main orbital sulci (medial, lateral and transverse) orbitofrontal sulcogyral patterns were classified within each hemisphere into one of four types (Chiavaras and Petrides, 2000; Chakirova *et al.,* 2010).

It was discovered that participants with autism had increased type II in the right hemisphere compared to healthy individuals ($p = 0.016$) and patients with first episode schizophrenia ($p = 0.040$). The distribution of type I

expression was significantly reduced in the first episode schizophrenia group ($p = 0.034$). Type III expression was significantly increased in the same group ($p = 0.018$) especially on the right side ($p = 0.031$).

In conclusion, the distribution of the orbitofrontal sulcogyral patterns was investigated in individuals from such diagnostic groups that included patients with bipolar disorder, autism spectrum disorder, those at high risk of developing bipolar disorder and schizophrenia, and unaffected relatives of bipolar disorder and schizophrenia. The OFC typing may have some utility in differentiating the conditions in cases posing diagnostic challenges. The orbitofrontal type I is mostly presented in healthy controls. Its reduced frequency in the patient groups allows to suggest that this type is expected to have 'the most healthiest' characteristics. Further, the orbitofrontal types II and III demonstrated their increased prevalence in patients with bipolar disorder (the left and right type III), schizophrenia (the right type III) and autism (the right type II). This means that type II and III could be associated with some features of the represented mental illnesses.

Figure 8.1. Distribution of orbitofrontal sulcogyral pattern in healthy controls, patients with first episode schizophrenia and ASD (autism-spectrum disorder): A, B, C = the right hemisphere. D, E, F = the left hemisphere. See **Figure 1.4** and **Chapters 1** and **3** for the description of the orbitofrontal sulcogyral types I, II, III and IV.



Recent study of autism-spectrum disorder by Watanabe and colleagues (2013) confirmed alteration of the orbitofrontal patterns in male participants with ASD.

8.2.2 The presence or absence of additional orbital sulci (posterior, intermediate orbital sulci or sulcus fragmentosus) might affect some of characteristics of the orbitofrontal sulcogyral patterns.

Given that this particular aspect of the orbitofrontal sulcogyral patterning was not a part of this study the statement above could only be supported by previously reported data. So far, there were only two publications found related to this topic. Roppongi and colleagues (2010) discovered the association of the posterior orbital sulcus absent and single variants with trait-anxiety and volume reduction in the right posterior-medial orbitofrontal region in patients with panic disorder. Further, Watanabe and colleagues (2013) reported an increased frequency of the absent posterior orbital sulcus variant in the right hemisphere in male individuals with autism spectrum disorder. These two unique reports allows to suggest that additional orbital sulci may be associated with mental illnesses and affect characteristics of the main orbitofrontal sulcogyral patterns (type I, II, III and IV). This could provide some explanation for the complex findings of the present study and may become a subject of interest for future research.

8.2.3 The orbitofrontal sulcogyral patterns and the paracingulate sulcus could share similar gender effects: males in the right hemisphere for both orbitofrontal and paracingulate morphology and females in the left hemisphere for both orbitofrontal and paracingulate morphology. This suggests that a gender effect could play a role in the prediction of mental illnesses and be a part of the predictive system of markers.

Two large cohorts (given group sizes in them): the Bipolar Family Study and the Edinburgh High Risk Study provided with an opportunity to explore the effect of gender on the distribution of the orbitofrontal sulcogyral patterns and paracingulate sulcus (See **Chapters 4** and **5** for details). Given that they are formed during the same period of neurodevelopment and, therefore, undergo the same environmental and genetic impact, it is possible to suggest that they might share at least some of their characteristics, including the gender effect.

A number of papers analysed the effect of gender on the anterior cingulate morphology (Vogt *et al.,* 1995; Yucel *et al.,* 2001; Leonard *et al.,* 2009; Rametti *et al.,* 2010) and only two papers examined this effect on the distribution of the orbitofrontal sulcogyral patterns (Uehara-Aoyama *et al.,* 2011; Watanabe *et al.,* 2013). Uehara-Aoyama and colleagues (2011) reported that the alteration of the orbitofrontal sulcogyral patterns in the right hemisphere in patients with schizophrenia originated in males rather than in females. Similarly, we found a gender effect on the distribution of the orbitofrontal morphology in the Edinburgh High Risk Study, the Bipolar Family Study and in the Psychosis Study. In the EHRS the distribution of ***type III in the right hemisphere*** was altered in male participants, while the distribution of the orbitofrontal ***type III in the left hemisphere*** differed in female individuals between the groups (See **Chapter 4** for details). In the Bipolar Family Study the difference in distribution of the orbitofrontal sulcogyral patterns between the groups was mostly originated in males in the right hemisphere and in females in the left hemisphere (See **Chapter 5** for details). In the Psychosis Study difference in distribution of the orbitofrontal sulcogyral patterns between healthy individuals and patients with schizophrenia, and between healthy individuals and patients with bipolar disorder in the right hemisphere was more likely to be originated in males, while difference in distribution of the orbitofrontal patterns in the left hemisphere seemed to be originated in female participants (See **Chapter 3**

for details). Further, Watanabe and colleagues (2013) reported that the distribution of the posterior orbital sulcus variant in the right hemisphere was altered in male individuals with the autism spectrum disorder. This indicates that even the distribution of the additional orbital sulci could be gender-related.

The paracingulate sulcus seems to share the same hemisphere - dependent gender effect with the orbitofrontal morphology. In the Edinburgh High Risk Study male control participants had a significantly increased frequency of the prominent PCS in the right hemisphere compared to both high - risk participants and patients with schizophrenia (See **Chapter 4** for details).

The further issue was the fact that the cingulate sulcus did not share a gender effect either with the paracingulate sulcus or the orbital sulcogyral patterns. The distribution of the cingulate pieces in the right hemisphere were more likely to be associated with female participants while the distribution of the orbitofrontal patterns and the paracingulate sulcus in the right hemisphere were more likely to be associated with males individuals (See **Chapters 3, 4,** and **5** for details).

8.2.4 Such structural features like possession of the symmetric orbitofrontal pattern distribution within the brain, continuity of the orbital and cingulate sulci, and an appearance of the prominent paracingulate sulcus variant in the individuals at high risk of developing schizophrenia or bipolar disorder might have a protective role.

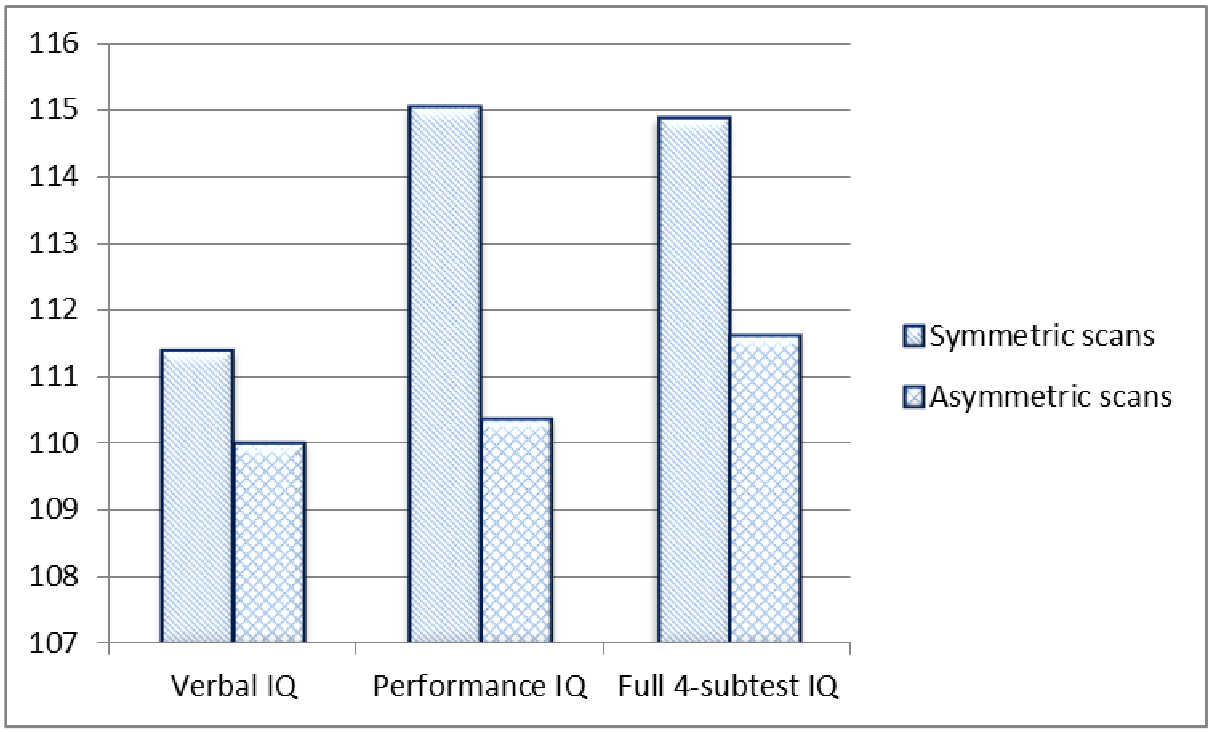
The symmetry – asymmetry scores related to the orbitofrontal and anterior cingulate morphology was another important finding of this study. The images were rated as symmetric if they had the orbitofrontal pattern in the right and left hemispheres or the same cingulate or paracingulate variant in

the right or left hemispheres (See **Chapters 3, 4** and **5** for details). In the EHRS healthy controls and high risk individuals who remained well tended to be more symmetric (44.4% and 44.2% of symmetric scans respectively) regarding to the orbitofrontal pattern distribution with no difference between the two groups, while patients with schizophrenia were more asymmetric (11.8% of symmetric scans) and differed from both controls and the high risk group (See **Chapter 4** for details). Consistent with this, in the Psychosis Study, while only 47% of healthy individuals and 42% of unaffected relatives of patients with schizophrenia had different orbitofrontal patterns in the right and left hemisphere (asymmetric orbitofrontal cortex), 73% of patients with schizophrenia were with asymmetric scans. Patients with bipolar disorder were more symmetric regarding the distribution of the orbitofrontal sulcogyral patterns than patients with schizophrenia. The rest of the groups were similar to healthy volunteers on the symmetry – asymmetry score (See **Chapter 3** for details).

Possession of the symmetric orbitofrontal cortex might be associated with better cognitive function as it is demonstrated in healthy individuals (See **Figure 8.2**) and in patients with bipolar disorder (See **Figure 8.3**). This suggests that symmetry of the orbitofrontal morphology could be an important characteristic of the system that predicts the development of schizophrenia or bipolar affective disorder.

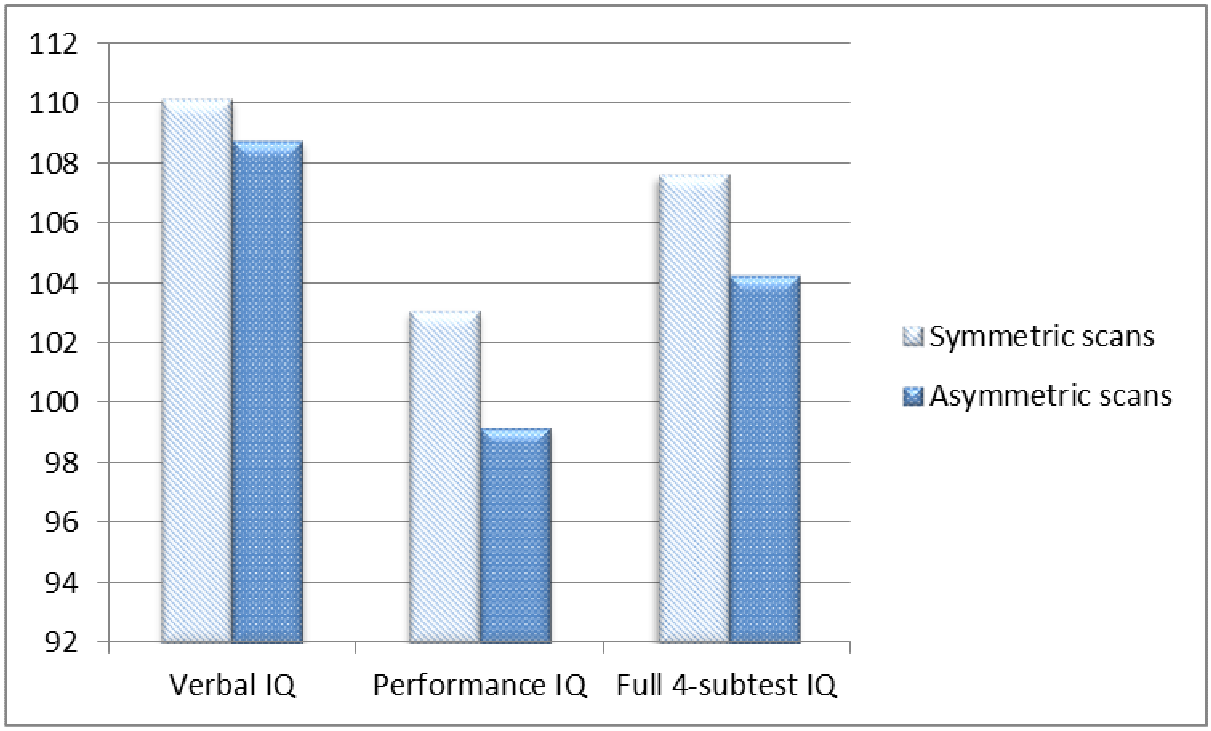
In order to analyze symmetry – asymmetry of the ACC, scans were rated as symmetric if they had the same variant of the cingulate sulcus (a single piece only or 'broken' into segments only) in the right and in the left hemispheres. In the EHRS we found that healthy individuals tended to be more symmetric (83.5% of symmetric scans), whereas patients with schizophrenia were more likely to be asymmetric (52.9% of symmetric scans) regarding to this score (See **Chapter 4** for details).

Figure 8.2. The WASI IQ scores in healthy controls with symmetric and asymmetric orbitofrontal morphology in the Psychosis Study. This bar chart demonstrates that those with symmetric scans perform better and score higher mean measures of full scale (Full 4-subtest), performance and verbal IQ for those with asymmetric scans.



This tendency of healthy individuals to have the same variants of the orbitofrontal sulcogyral patterns and the same variant of the cingulate sulcus in the right and left hemisphere allowed the suggestion that the symmetric distribution of the anterior cingulate and orbitofrontal morphology might play a protective role or reflect certain qualities of a healthy brain. This means that it might be less risky (regarding to the development of mental illness) to have the orbitofrontal type III (or type II) in both left and right hemispheres (symmetric scan) than having type III (or type II) in only one of the hemispheres (asymmetric scan).

Figure 8.3. The WASI IQ scores in patients with bipolar disorder and a family history of bipolar disorder only with symmetric and asymmetric orbitofrontal morphology, the Psychosis Study. This bar chart demonstrates that those with symmetric scans perform better and score higher mean measures of full scale (Full 4-subtest), performance and verbal IQ for those with asymmetric scans.



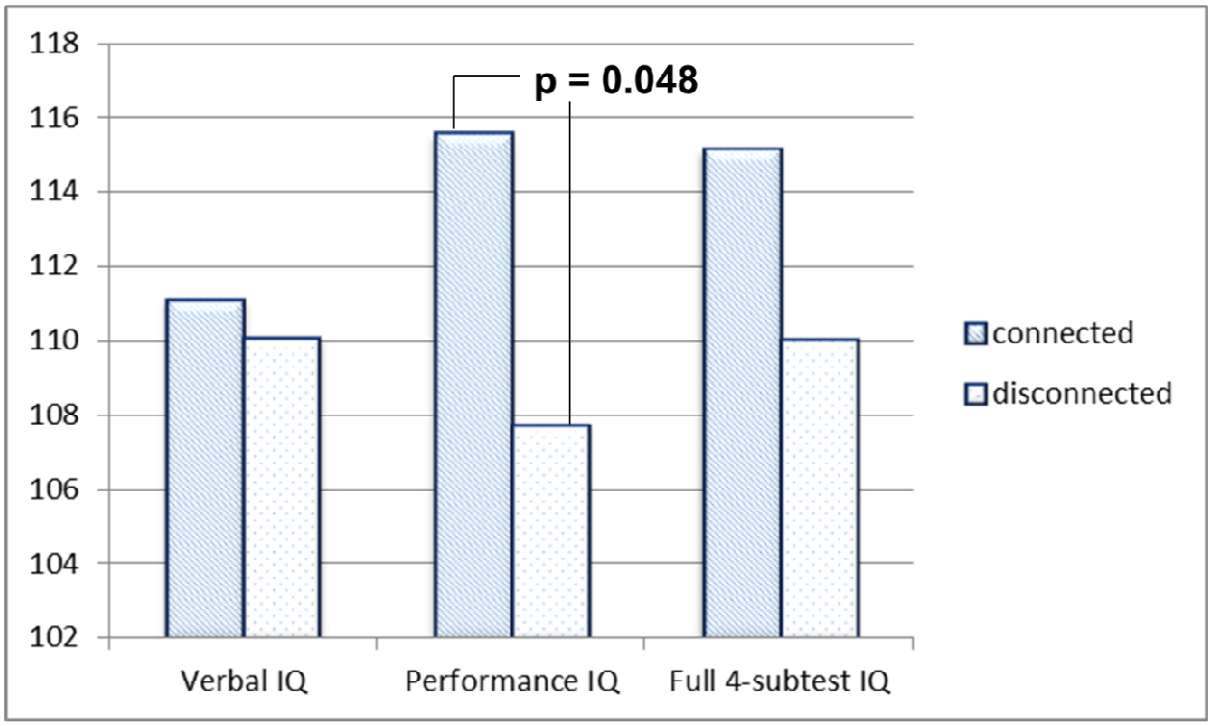
Apart the symmetry – asymmetry issue there is a subject of continuity of orbital or cingulate sulci when healthy individuals were more likely to have a single continuous cingulate sulcus in both hemispheres, while patients with schizophrenia and unaffected relatives of patients with bipolar disorder tend to have a 'disconnected' ('broken') cingulate sulcus with 2 or 3 pieces (segments). The unaffected relatives of patients with schizophrenia were more likely to have the cingulate sulcus as one piece while patients with schizophrenia had mostly disconnected CS in the right hemisphere.

Possession of the continuous cingulate sulcus might also be associated with better cognitive function as it is demonstrated in healthy individuals (See **Figure 8.4**) from the Psychosis Study. This suggests that continuity of the cingulate sulcus might play a role as a part of the system that predicts the development of schizophrenia or bipolar affective disorder.

Further, there was a gender effect found in the distribution of the cingulate sulcus. Female healthy individuals had an increased frequency of the connected CS (presented as one piece) while female unaffected relatives of patients with schizophrenia were more likely to have an increased frequency of the disconnected CS (presented in many pieces) in the right hemisphere.

With regards to the distribution of the paracingulate sulci, unaffected relatives of patients with schizophrenia tend to have an increased prevalence of the prominent paracingulate sulcus variant in the left hemisphere compared to the schizophrenia patients themselves. Similarly, unaffected relatives of patients with bipolar disorder had an increased prevalence of the prominent paracingulate sulcus in the left hemisphere when compared to patients with bipolar disorder. These suggest that the prominent paracingulate sulcus variant in the left hemisphere might be an indicator of reduced risk of development of schizophrenia or bipolar disorder. Moreover, there could be a gender effect found on the prevalence of the prominent PCS as the female unaffected relatives of patients with schizophrenia had an increased frequency of the prominent paracingulate sulcus variant in the left hemisphere compared to its distribution in female patients themselves. In contrast, female patients with bipolar disorder had an increased frequency of the PCS absent variant and a reduced frequency of the PCS prominent variant compared to their female unaffected relatives. Similar differences were correct for male individuals in the right hemisphere.

Figure 8.4. The WASI IQ scores in healthy controls with the connected and disconnected cingulate sulcus morphology in the Psychosis Study. This bar chart demonstrates that healthy controls with the connected cingulate sulcus variant in the left hemisphere performed better and scored higher the mean measures of full scale (Full 4-subtest), performance and verbal IQ compared to those controls with the disconnected CS variant in the left hemisphere.



8.2.5 Each orbitofrontal pattern might be associated with certain brain functional and structural characteristics. These associations include structural brain alterations, changes in brain activation, connectivity, personality traits and altered cognitive functions that could be evident even in healthy controls. The associations of similar orbitofrontal sulcogyral patterns in the right and in the left hemispheres could vary between each other (the orbitofrontal type III in the left hemisphere may

have associations different from those of the orbitofrontal type III in the right hemisphere).

Structural and functional abnormalities associated with the orbitofrontal morphology were examined in healthy participants from the Bipolar Family Study (See **Chapter 6** and **7** for details) who were without a family or personal history of mental illnesses, a history of brain injury or drug addiction. Those participants were subdivided into groups according to the type of the orbitofrontal pattern in both right and left hemisphere (symmetric scans; See **Chapter 1** and **Chapter 3** for details). Additionally, healthy individuals were subdivided on the basis of the distribution of the orbitofrontal sulcogyral types in the right or in the left hemisphere separately in order to analyse whether the results from symmetric scans were originated from the orbitofrontal morphology differences in particular hemispheres.

The grey matter density was compared in those forty healthy volunteers from the Bipolar Family Study who possessed the orbitofrontal types I, II and III in both left and right hemispheres. It was discovered that healthy individuals with the orbitofrontal type III had reduced grey matter density in the right orbitofrontal area (the superior (BA 10) and middle frontal (BA 10) gyri), right medial frontal gyrus (BA 9), ***the left and right anterior cingulate regions*** (BA 32), and that these results derived from the grey matter differences associated with the orbitofrontal morphology in the right hemisphere. Importantly, this VBM results in **Chapter 6** was supported by the reduction of cortical thickness in the right medial orbitofrontal area in the participants with ***type III in the right hemisphere*** compared to healthy volunteers with the orbitofrontal type I.

In the Edinburgh High Risk Study the orbitofrontal ***type III in the right hemisphere*** was found to be associated with the smaller volume of the right caudate nucleus in male participants at high genetic risk of developing

schizophrenia. Further, male participants at high risk of developing schizophrenia with orbitofrontal ***type III in the left hemisphere*** had larger volume of the left thalamic nucleus (See **Chapter 4** for details).

In the Bipolar Family Study participants at high risk of developing bipolar disorder with the orbitofrontal ***type III in the right hemisphere*** had an increased volume of the isthmus of ***the cingulate gyrus in the left hemisphere***. Further, participants at high risk of developing bipolar disorder with the orbitofrontal ***type III in the left hemisphere*** had smaller volume of ***the left posterior cingulate cortex***, with this association being originated in females (See **Chapter 5** for details).

Brain activation differences were analysed using fMRI technique in those healthy individuals from the Bipolar Family Study who had the same orbitofrontal pattern in both the right and the left hemispheres (symmetric scans; See **Chapters 1, 3** and **7** for details).

Functional MRI revealed increased brain activation in healthy individuals with the orbitofrontal ***type III*** compared to those healthy volunteers with the orbitofrontal type I in the following areas: ***the right posterior cingulate gyrus*** (BA 31), right caudate tail for the sentence completion versus baseline contrast and in ***the left anterior cingulate*** (BA 32) area for the parametric contrast (See **Chapter 7** for details). These results are particularly interesting knowing that both cingulate cortex and caudate nucleus are connected to the orbitofrontal region. Crucially, there was a decrease of grey matter density found in the BA 32 region for the same comparison using the VBM method (Type III versus Type I; See **Chapter 6** for details). Brodmann Area 32 is the dorsal part of the anterior cingulate and is known to be active during the Stroop task (See **Chapter 4** for details). The structural and BOLD-signal differences between those with the orbitofrontal type I and type III especially involving Stroop-associated area might provide with an explanation of the

performance differences during the Stroop test among those with the orbitofrontal types I and III (See **Chapter 4** for further details on the Stroop test performances).

These are important findings that demonstrated differences occurring even within healthy controls between those with type III and those healthy participants with the orbitofrontal type I. The fact that orbitofrontal sulci and underlying white matter form during the same period of gestation suggests that the orbitofrontal type III is associated with the grey matter and BOLD signal abnormalities, probably due to genes and environmental influences. Given these findings and an increased frequency of the orbitofrontal type III in patients with schizophrenia and bipolar disorder this pattern could be a marker of neurodevelopmental problems. Although, type III is not a cause of the condition but rather it is its silent sign indicating underlying problems.

The VBM analysis revealed that healthy individuals with the orbitofrontal type II in both hemispheres had reduced grey matter density in the left orbitofrontal cluster that included the left middle frontal gyrus (BA 11), superior frontal gyrus (BA 11) and inferior frontal gyrus (BA 47), when compared to those controls with the orbitofrontal type I. This cluster was originated in those participants with the orbitofrontal type II in the right hemisphere and survived covariating for gender, handedness and the NART IQ scores. Furthermore, healthy individuals with the orbitofrontal type II in the left hemisphere had reduced white matter density in the middle frontal gyrus when compared to healthy individuals with type I in the left hemisphere (See **Chapter 6** for details).

Unlike with structural MRI analysis, functional MRI did not reveal any brain activation difference in healthy individuals with the orbitofrontal type I and II in both hemispheres. The possible explanation is the limitations of the fMRI

method with regards to examining the orbitofrontal region including areas BA 11 and BA 47/12 due to the large susceptibility artefacts.

The VBM analysis did not reveal any difference in the grey matter density between controls with the orbitofrontal type II and type III. However, there were some findings for this comparison obtained using fMRI. The areas of activation differences included the left thalamus, left anterior nucleus, right caudate tail, the right and left caudate body, right insula (BA 13), right posterior cingulate gyrus (BA 23, 31), right precuneus (BA 31), left lentiform nucleus, putamen, ***left cingulate gyrus*** (BA 32), ***right anterior cingulate gyrus*** (BA 24, 32), the right superior frontal gyrus (BA 8, 9) and middle frontal gyrus (BA 8. 9) for the sentence versus baseline contrast (See **Chapter 7** for details).

Associations between the orbitofrontal and cingulate regions are particularly important finding for this study given that the combination of their structural variants may improve positive and negative predictive value and might allow excluding those individuals at high risk that have better chances to remain well with 92 - 96% of accuracy (See **Chapters 4** and **5** for details).

In the EHRS individuals at high risk of developing schizophrenia who had the orbitofrontal ***type III in the right hemisphere*** had increased fronto - parietal connectivity compared to those without. In the Bipolar Family Study healthy individuals with the orbitofrontal type III had reduced connectivity between the right lateral orbitofrontal cortex and left cingulate gyrus when compared to those with type I (See **Appendix IV** for details on the PPI analysis). There was an increased connectivity found between the left medial orbitofrontal cortex and right cingulate gyrus in the Bipolar Family Study in participants with the orbitofrontal type III when compared to those healthy individuals with type I (parametric contrast).

Neuropsychological associations of the orbitofrontal sulcogyral patterns were examined in the study of seven groups, in those at high risk of developing schizophrenia and in those at high risk of developing bipolar disorder. There were some commonalities observed among those associations that were strikingly consistent throughout all three cohorts.

First of all, it seems like those with the orbitofrontal sulcogyral type III might experience problems with inhibitory control when there is necessity to stop and switch the verbal domain given their performances during the Stroop Colour Word Test and The Rey Auditory - Verbal Learning Test in the Edinburgh High Risk Study, the Hayling Sentence Completion task in the Bipolar Family Study, and the verbal IQ and the Hayling Sentence Completion task in the Psychosis Study. There were also associations found in the orbitofrontal sulcogyral patterns with the executive tasks (the IDED) and with personality traits.

The results of the neuropsychological associations of the orbitofrontal morphology suggests that despite the wider distribution of the orbitofrontal type I in healthy population (was discovered in 56% of healthy hemispheres, according to Chiavaras and Petrides, 2000) this pattern is not the 'brightest' between the orbitofrontal patterns. The mostly connected type II (was discovered in 30% of healthy hemispheres) scored higher in the WASI IQ in healthy individuals (even if difference was not significant). For example, in the healthy individuals of the Bipolar Family Study the verbal IQ scores were: mean = 103.92 (SD = 12.321) in those with type I, mean = 112.19 (SD = 8.867) in those with type II, and mean = 106.00 (SD = 10.376) in those with type III in the right hemisphere; and mean = 105.52 (SD = 10.779) in those with type I, mean = 112.88 (SD = 12.539) in those with type II, and mean = 97.91 (SD = 16.009) in those with type III in the left hemisphere. Similarly, in healthy controls from the Psychosis Study the WASI verbal IQ scores were: mean = 108.29 (SD = 13.077) in those with type I, mean = 118.30 (SD =

8.015) in those with type II, and mean = 105.80 (SD = 17.598) in those with type III in the right hemisphere. Moreover, the schizophrenia patients with the orbitofrontal type II seemed to have better chances to have their cognitive functions preserved compared to patients with the other orbitofrontal patterns. In the schizophrenia patients from the study of seven groups the verbal IQ scores were: mean = 98.36 (SD = 12.971) in those with type I, mean = 107.33 (SD = 9.913) in those with type II, and mean = 95.38 (SD = 8.228) in those with type III in the right hemisphere.

In the EHRS male participants at high risk of developing schizophrenia with the orbitofrontal ***type III in the right hemisphere*** performed poorly during the Stroop test. In the BFS individuals at high risk of developing bipolar disorder with the orbitofrontal ***type III in the right hemisphere*** experienced more difficulties while performing reversal trials of the IDED task than participants with any other orbitofrontal patterns in the right hemisphere. In the EHRS the female participants at high risk of developing schizophrenia with ***type III in the right hemisphere*** scored significantly less or recalled fewer words during the postdistractor trial of the Rey Auditory - Verbal Learning Test compared to both females without type III and male participants with or without the orbitofrontal type III in the right hemisphere. In the BFS during the Hayling Sentence Completion Test male high risk participants of developing bipolar disorder with the orbitofrontal ***type III in the right hemisphere*** and female individuals with the orbitofrontal ***type III in the left hemisphere*** were inclined to use less frequent and less appropriate words to complete the sentence.

In the EHRS an association was found between the presence of the orbitofrontal type III in either hemisphere and the SIS psychotic symptoms factor rating, which was that the participants with type III had a higher score on this factor. The SIS psychotic symptoms factor may represent a greater range of symptoms including psychotic – like phenomena, magical thinking

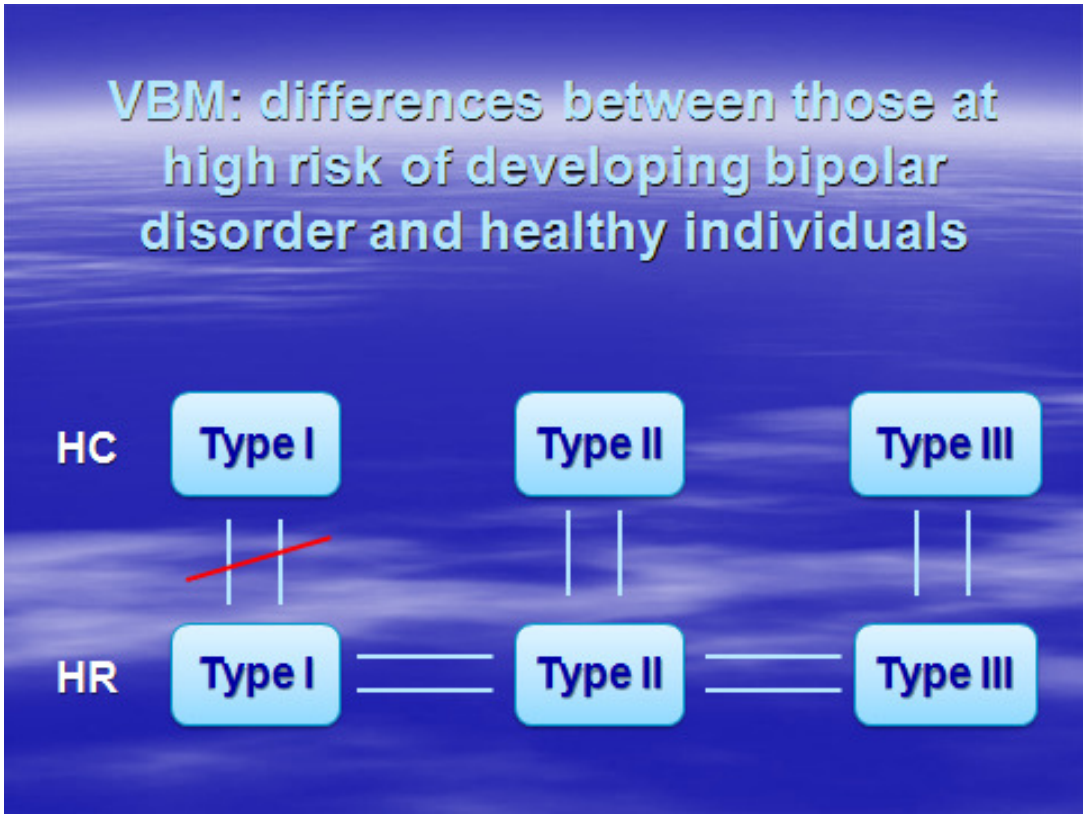
and suspiciousness. In the BFS the orbitofrontal ***type III in the right hemisphere*** was found to be associated with the higher Hamilton Rating Scale for Depression scores in the female participants at high risk of developing bipolar disorder.

In the BFS male high risk participants of developing bipolar disorder with the orbitofrontal type III in the right and in the left hemisphere scored less in openness to experience (and, therefore, tend to be more conventional and resistant to change), while females with the orbitofrontal ***type III in the left hemisphere*** scored more in conscientiousness (a tendency to be dutiful, motivated for achievements, to be able to demonstrate planned behaviour).

8.2.6 The orbitofrontal sulcogyral patterns might change some of their characteristics in diagnostic groups (patients with schizophrenia and bipolar disorder and their unaffected relatives, and in those at high risk of developing schizophrenia and bipolar disorder) compared to healthy individuals.

This statement is based on the comparison of the orbitofrontal patterns between two groups of the Bipolar Family Study (See **Figure 8.5**). The only difference that was found between healthy controls and those at high risk of developing bipolar disorder was originating from the participants with the orbitofrontal type I. This data is not a part of this thesis and will not be presented here.

Figure 8.5. This figure demonstrates that the only difference in the grey matter density was found between individuals with the orbitofrontal type I when two groups were compared using VBM. HC = Healthy controls. HR = those at high risk of developing bipolar disorder. Types I, II and III refer to the orbitofrontal sulcogyral patterns. HC and HR were subdivided into three group with types I, II and III in both left and right hemispheres. Comparison by using VBM analysis of these subgroups between HC and HR revealed that only HC and HR with type I in both hemispheres differed between each other significantly. Within HR there was no difference between subgroups as between type II and type III HC and HR. Results of subgroup comparison in HC explained in details in Chapter 6 of this thesis. In conclusion, all the found difference between HC and HR seems to be originating in those with type I that becomes 'less healthy' in HR.



8.2.7 Orbitofrontal patterns could be associated and/or connected to the paracingulate sulcus. The right orbitofrontal cortex might be connected to the left orbitofrontal cortex and vice versa. The right orbitofrontal cortex could be associated not only to the right ACC but also to the left anterior cingulate area. Likewise, the left orbitofrontal cortex might be associated not only to the left ACC, but also to the right anterior cingulate area.

The left and right orbitofrontal cortex could be connected to each other through forceps minor and an anterior portion (genu) of the corpus callosum.

There is an indication in this data on the possible connection between the orbitofrontal and anterior cingulate morphology in the right and left hemispheres in all three cohorts. For example, healthy individuals with ***type II in the left hemisphere*** were more likely to be in a possession of the connected ***cingulate sulcus in the right hemisphere*** compared to those participants that were without the orbitofrontal type II in the left hemisphere. The cingulum contains fibers that connect the cingulate and orbitofrontal cortices, runs within the cingulate gyrus and plays a role in attention, emotions and memory (Amodio and Frith, 2006; Broyd *et al.,* 2009).

In the Psychosis Study patients with bipolar disorder had the orbitofrontal sulcogyral patterns being associated with the cingulate cortex in the same hemisphere as well as in the opposite one. The bipolar patients with the orbitofrontal type III in the right hemisphere were more likely to have the prominent paracingulate sulcus in the right hemisphere compared to those patients with bipolar disorder that were without the orbitofrontal type III in the right hemisphere. There was also an association found between the orbitofrontal type III in the left hemisphere and the right prominent PCS in such a way that those bipolar patients with the orbitofrontal type III in the left hemisphere were more likely to have the prominent paracingulate sulcus in

the right hemisphere compared to those patients with bipolar disorder that were without the orbitofrontal type III in the left hemisphere.

In the Bipolar Family Study participants at high risk of developing bipolar disorder with the orbitofrontal ***type III in the right hemisphere*** had an increased volume of the isthmus of the cingulate gyrus in the left hemisphere. Further, participants at high risk of developing bipolar disorder with the orbitofrontal ***type III in the left hemisphere*** had smaller volume of the left posterior cingulate cortex, with this association being originated in females.

In the EHRS association was found between the orbitofrontal ***type III in the left hemisphere*** and the paracingulate sulcus in the healthy female individuals in such a way that those with the orbitofrontal type III in the left hemisphere were more likely to have the paracingulate sulcus present in the left hemisphere as well.

There was an interesting association observed between the connectivity of the orbitofrontal morphology and the connectivity of the anterior cingulate morphology. For example, healthy individuals with the orbitofrontal type I (half-connected, half-disconnected pattern) in the left hemisphere were more likely to be in a possession of the connected cingulate sulcus in the left hemisphere while those healthy individuals with the orbitofrontal type III (mostly disconnected pattern) in the left hemisphere were more likely to be in a possession of the disconnected cingulate sulcus in the left hemisphere. Even the schizophrenia patients with the orbitofrontal type I in the left hemisphere were more likely to be in a possession of the connected cingulate sulcus in the right hemisphere compared to those patients with schizophrenia that were without the orbitofrontal type I in the left hemisphere. The bipolar patients with the orbitofrontal type I and/or without the orbitofrontal type II in the right hemisphere were more likely to have the connected cingulate sulcus in the right hemisphere compared to those

patients with bipolar disorder that were without the orbitofrontal type I or with the orbitofrontal type II in the right hemisphere. Further, unaffected relatives of bipolar patients with the orbitofrontal type I and/or without the orbitofrontal type III in the right hemisphere were more likely to have the connected cingulate sulcus in the left hemisphere compared to those unaffected relatives of patients with bipolar disorder that were without the orbitofrontal type I or with the orbitofrontal type III in the right hemisphere. This suggests that the 'connectivity-connectivity' associations between the orbitofrontal and cingulate morphology may not be diagnosis related but be a characteristic of the orbitofrontal sulcogyral patterns and cingulate sulcus variants themselves.

8.2.8 There could be an interaction between the orbitofrontal sulcogyral patterns located in the right and in the left hemisphere within one brain. This might be correct even for the symmetric orbitofrontal cortex. In the symmetric brain two identically rated orbitofrontal patterns could potentially reduce an effect of each other's presence. In this sense, it would be safer to have the symmetric brain with the orbitofrontal type III in the right and in the left hemisphere than to have an asymmetric brain with type III in the one of the hemispheres only.

This statement is mostly based on the observation of the grey matter density, brain activation differences and neuropsychological task performances observed when symmetric and asymmetric scans of healthy individuals from the Bipolar Family Study were compared. Additionally see also **Figures 8.2** and **8.3** of this **Chapter 8**. This data is not a part of this thesis.

8.2.9 The connection between the orbitofrontal and cingulate morphology might allow a combination of these patterns into new system that could predict the development of mental illnesses including schizophrenia and bipolar affective disorder. In this system

several patterns might be united and a predictive value could be defined as a value of a whole system (the combination of the patterns) rather than a predictive value of one pattern separately. In this system the orbitofrontal sulcogyral patterns might have a senior position towards the paracingulate sulcus as unlike the paracingulate sulcus the orbital sulci are always present. This predictive system might include an effect of the specific genes and gender.

In the EHRS combination of the orbitofrontal type III in the right hemisphere and the prominent paracingulate sulcus variant in the left hemisphere secured better predictive value than when these patterns were analysed separately: for type III in the right hemisphere negative predictive value was 89.9%, for the left prominent PCS negative predictive value was 93.4%, combination of them both provided with the negative predictive value of 95.5% (See **Chapter 4** for details).

In the BFS combination of the orbitofrontal and paracingulate morphology provided with better predictive value than the orbitofrontal or paracingulate morphology on its own with the best results when the orbitofrontal type III in the left hemisphere and the absent PCS variant in the right hemisphere were combined (92%) (See **Chapter 5** for details). Adding to this system the DISC1 SNP rs6675281 (Leu607Phe) improves the negative predictive value to 100%. This finding and the striking persistence of a gender effect on the distribution of the orbitofrontal sulcogyral patterns suggests that an effect of the specific genes and gender might be included into the predictive system.

8.2.10 The orbitofrontal sulcogyral patterns could be associated with genes including dysbindin and DISC1.

Evidence suggests a genetic impact on the orbitofrontal morphology, with the orbitofrontal sulcogyral patterns being influenced by a number of genes

including dysbindin and DISC1. Cerasa and colleagues (2010) reported a significant association of the C-A-T dysbindin schizophrenia - risk haplotype carrying with the structural differences in the right medial orbitofrontal cortex in healthy individuals. With the threshold being lowered, the risk – haplotype carriers showed a more pronounced thickening of the right cingulate cortex as well as the left lateral and medial orbitofrontal area.

Further, the orbitofrontal cortex was previously found to be associated with personality traits (Fujiwara *et al.,* 2008), when with increasing neuroticism the left lateral orbitofrontal cortex was found to be reflecting relative rather than absolute loss. On the contrary, with increasing introversion, the right lateral orbitofrontal cortex was associated with absolute rather than relative losses. In the Bipolar Family Study male high risk participants of developing bipolar disorder with the orbitofrontal type III in the right and in the left hemisphere scored less in openness to experience (and, therefore, tend to be more conventional and resistant to change), while females with the orbitofrontal ***type III in the left hemisphere*** scored more in conscientiousness (a tendency to be dutiful, motivated for achievements, to be able to demonstrate planned behaviour). Moreover, Roppongi and colleagues (2010) discovered the association of the posterior orbital sulcus absent and single variants with trait-anxiety and volume reduction in the right posterior-medial orbitofrontal region in patients with panic disorder indicating that even additional sulci could be linked to some personality traits.

Further, DISC1 was previously found to be associated with the personality traits. Tomppo and colleagues (2009 b) reported the connection between the carrying of the minor DISC1 allele of marker rs821577 and higher scores on social anhedonia, and between rs821633 and lower scores on social anhedonia dependent on the absence of the minor alleles of markers rs1538979 and rs821577.

Given that the orbitofrontal cortex was found to be associated with various personality traits, DISC1 was linked with anhedonia, and dysbindin was related to the differences in cortical thickness in the right medial orbitofrontal cortex, it is possible to suggest that the orbitofrontal sulcogyral patterns might have associations with genes including dysbindin and DISC1.

8.3 Strength of the study

This research project is intended to contribute to a new emerging field dedicated to the orbitofrontal sulcogyral patterns. There is a growing amount of publications in this area coming from the Harvard Medical School (Boston, USA), Yokohama City University, School of Medicine (Yokohama, Japan) and the University of Florida (USA). They discuss association of the orbitofrontal sulcogyral patterns with mental illnesses, including schizophrenia, autism-spectrum and panic disorder, association of the orbitofrontal sulcogyral patterns with the grey matter volume and personality traits (Nakamura *et al.,* 2007; Nakamura *et al.,* 2008; Roppongi *et al.,* 2010; Takayanagi *et al.,* 2010; Uehara-Aoyama *et al.,* 2011; Watanabe *et al.,* 2013).

In the present study a remarkable opportunity was provided to examine the orbitofrontal sulcogyral patterns in a number of large cohorts and compare distribution of the orbitofrontal patterns and their structural and functional associations between different studies. The diagnostic groups included patients with bipolar disorder, schizophrenia, autism, unaffected relatives of patients with bipolar disorder and schizophrenia and those at high risk of developing schizophrenia or bipolar disorder. The results of the analyses were reported in a form of the theory of the predictive associations of the orbitofrontal morphology. Importantly, a new way to predict development of mental illnesses was suggested using combination of the orbitofrontal patterns and the paracingulate sulcus variants.

8.4 Limitations of the study

There are a number of difficulties to be concern either when applying manual sulci identification protocol or when involving automatic sulci recognition software. Firstly, a variability of sulcogyral morphology across individuals, which is particularly well - known in the orbitofrontal area, might affect the results of manual sulci identification. This is why most of the rating was done twice by two researchers independent to each other. Further, the highly variable junctions between sulci as well as the spatial relationship between sulci and gyri of the cerebral cortex might also increase the complexity of the identification process for the automatic sulci recognition pipeline. This might complicate a further application of both manual and automatic protocols.

Another limitation of this study was related to a relatively small number of the participants in some groups (relatively to the type of study presented in this thesis). For this reason, there could be missing or difficult to interpret findings related to neuropsychological associations of the orbitofrontal sulcogyral patterns within each group. Moreover, the sample size (particularly, those with the orbitofrontal type III) limited possibilities to examine interactions between different orbitofrontal patterns in the right and in the left hemisphere.

Finally, there is an issue of multiple comparisons arising from the examination of neuropsychological associations. However, it should be noted that the subject of analyses in this thesis is relatively novel and, therefore, most of the testing was performed for the first time. Further, this thesis is a combination of a number of studies. In each of these studies the hypothesis was clearly formulated, examined and confirmed (Bender and Lange, 2001; Schochet, 2008). Moreover, the findings in **Chapters 6** and **7** were corrected for multiple comparisons, as well as the distribution of the OFC and ACC in **Chapters 3**, **4** and **5.** The neuropsychological associations were mostly exploratory, they were examined in order to understand the data (Schochet,

2008), and were organised in such a way that allowed a search for patterns. There are different methods of such search, choice of which is dependent on particular data (Tetko and Villa, 2001; Bunke and Riesen, 2011; Adame et al., 2012; Anderson, 2012; Long et al., 2012; Haxby, 2012). Investigating the neuropsychological associations was an attempt to discover patterns, repetitive results in this large data and to transform it into clear, understandable and useful structure. Such exploration of three cohorts was important as it presented in itself as a remarkably rare opportunity (over 550 scans accompanied by detailed psychological assessment and fMRI). However, specificity of data distribution, small sample size after subdividing initial groups by the orbitofrontal pattern variants and gender, required original approach. The pattern identification process is a respectful previously published method (Schochet, 2008). Importantly, attention was paid to those results that were replicable in at least two cohorts (for example, an increased frequency of the orbitofrontal type III in the right hemisphere in patients with schizophrenia and in those at high risk of developing schizophrenia who became ill; See **Chapter 3** and **4** for details), and to persistent tendencies (for example, the associations of the orbitofrontal patterns with the verbal tests in all three cohorts). These findings could be used to identify new hypotheses that might become subject to future studies and could be tested against the larger data set. Such exploratory analyses are necessary as this might help to avoid testing of an inaccurate hypothesis, application of inappropriate methods and obtaining false negative results. The theory of predictive associations of the orbitofrontal sulcogyral patterns is a combination of the conclusions and hypotheses that were developed on the basis of the findings described in previous chapters of this thesis.

8.5 Suggestions for future research

- Examining an effect of additional orbital sulci on characteristics of the main orbitofrontal sulcogyral patterns;

- Analysing the distribution of the orbitofrontal patterns in various diagnostic groups including larger sample of individuals with autism-spectrum disorder;
- Investigating the association of the orbitofrontal morphology with genes;
- Analysing the orbitofrontal morphology in the larger study in order to explore possible interactions between orbitofrontal patterns in the right and left hemisphere;
- Completing the theory of predictive associations via further development of system of markers that could predict the development of mental illnesses and via identification and improvement of positive predictive value of such system.

Bibliography

A

Adame, J.A., Notario, A., Villanueva, F., Albaladejo, J. 2012. Application of cluster analysis to surface ozone, NO2 and SO2 daily patterns in an industrial area in Central-Southern Spain measured with a DOAS system. *Science of the Total Environment* 429: 281 – 291.

Addington, A.M., Gornick, M.C., Shaw, P., Seal, J., Gogtay, N., Greenstein, D., Clasen, L., Coffey, M., Gochman, P., Long, R., Rapoport, J.L. 2007. Neuregulin 1 (8p12) and childhood-onset schizophrenia: susceptibility haplotypes for diagnosis and brain developmental trajectories. *Molecular Psychiatry* 12 (2): 195 - 205.

Akiskal, H.S., Mendlowicz, M.V., Jean-Louis, G., Rapaport, M.H., Kelsoe, J.R., Gillin, J.C., Smith, T.L. 2005 a. TEMPS - A: Validation of a short version of a self-rated instrument designed to measure variations in temperament. *The Journal of Affective Disorders* 85 (1 - 2): 45 – 52.

Akiskal, H.S., Akiskal, K.K., Haykal, R.F., Manning, J.S., Connor, P.D. 2005 b. TEMPS - A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. *The Journal of Affective Disorders* 85 (1 - 2): 3 - 16.

Allin, M.P., Marshall, N., Schulze, K., Walshe, M., Hall, M.H., Picchioni, M., Murray, R.M., McDonald, C. 2010. A functional MRI study of verbal fluency in adults with bipolar disorder and their unaffected relatives. *Psychological Medicine* 40: 2025 – 2035.

Allman, J.M., Tetreault, N.A., Hakeem, A.Y., Manaye, K.F., Semendeferi, K., Erwin, J.M., Park, S., Goubert, V., Hof, P.R. 2010. The von Economo neurons in frontoinsular and anterior cingulate cortex in great apes and humans. *Brain Structure and Function* 214: 495 – 517.

Altshuler, L.L., Bookheimer, S.Y., Townsend, J., Proenza, M.A., Eisenberger, N., Sabb, F., Mintz, J., Cohen, M.S. 2005. Blunted activation in orbitofrontal cortex duringmania: a functionalmagnetic resonance imaging study. *Biological Psychiatry* 58: 763 – 769.

Amaral, D.G., Price, J.L. 1984. Amygdalo-cortical projections in the monkey (Macaca fascicularis). *The Journal of Comparative Neurology* 230: 465 – 496.

American Psychiatric Association. 1994. *Diagnostic and statistical Manual of Mental Disorders, Fourth Edition*. Washington, D.C: American Psychiatric Association.

Amodio, D.M., Frith, C.D. 2006. Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience* 7: 268 – 277.

An, X., Bandler, R., Ongur, D., Price, J.L. 1998. Prefrontal cortical projections to longitudinal columns in the midbrain periaqueductal gray in macaque monkeys. *Journal of Comparative Neurology* 401 (4): 455 - 479.

Anderson, J.R. 2012. Tracking problem solving by multivariate pattern analysis and Hidden Markov Model algorithms. *Neuropsychologia* 50: 487 – 498.

Andreasen, N.C., Arndt, S., Swayze, V. 2nd, Cizadlo, T., Flaum, M., O'Leary, D., Ehrhardt, J.C., Yuh, W.T. 1994. Thalamic abnormalities in schizophrenia visualised through magnetic resosnance image averaging. *Science* 266 (5183): 294 – 298.

Armstrong, E., Schleicher, A., Omran, H., Curtis, M., Zilles, K. 1995. The ontogeny of human gyrification. *Cerebral Cortex* 5: 56 – 63.

Arnone, D., Cavanagh, J., Gerber, D., Lawrie, S.M., Ebmeier, K.P., McIntosh, A.M. 2009. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. *The British Journal of Psychiatry* 195 (3): 194 - 201.

Aron, A.R., Poldrack, R.A. 2005. The Cognitive Neuroscience of Response Inhibition: Relevance for Genetic Research in Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry* 57 (11): 1285 – 1292.

Arts, B., Jabben, J., Krabbendam, L., van Os, J. 2008. Meta - analyses of cognitive functioning in euthymic bipolar patients and their first - degree relatives. *Psychological Medicine* 38: 771 - 785.

Ashburner, J., Friston, K.J. 2000. Voxel-Based Morphometry – the methods. *NeuroImage* 11 (6 Pt 1): 805 – 821.

B

Bachevalier, J., Loveland, K.A. 2006. The orbitofrontal–amygdala circuit and self regulation of social–emotional behavior in autism. *Neuroscience and Biobehavioral Reviews* 30: 97 – 117.

Backlund, L., Nikamo, P., Rosvall, L., Frisen, L., Landen, M., Ladanayi, J., Träskman-Bendz, L., Ågren, H., Schalling, M., Ösby, U. 2008. Association between G72/30 haplotypes and bipolar disorder in a Swedish sample. *European Psychiatry* 23 (2): S225.

Baker, S.C., Frith, C.D., Dolan, R.J. 1997. The interaction between mood and cognitive function studied with PET. *Psychological Medicine* 27: 565 – 578.

Barbas, H., Pandya, D.N. 1989. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *The Journal of Comparative Neurology* 286: 353 – 375.

Barch, D.M., Braver, T.S., Akbudak, E., Conturo, T., Ollinger, J., Snyder, A. 2002. Anterior cingulate cortex and response conflict: effects of response modality and processing domain. *Cerebral Cortex* 11: 837 – 848.

Baron-Cohen, S., Ring, H., Moriarty, J., Schmitz, B., Costa, D., Ell, P. 1994. Recognition of mental state terms. Clinical findings in children with autism and a functional neuroimaging study of normal adults. *The British Journal of Psychiatry* 165 (5): 640 – 649.

Baron-Cohen, S. 1995. *Mindblindness: An essay on autism and theory of mind.* Cambridge, MA: MIT Press/Bradford Books.

Bartholomeusz, C.F., Box, G., Van Rooy, C., Nathan, P.J. 2003. The modulatory effects of dopamine D and D receptor function on object working memory in humans. *The Journal of Psychopharmacology* 17: 9 – 15.

Batardiere, A., Barone, P., Knoblauch, K., Giroud, P., Berland, M., Dumas, A.M., Kennedy, H. 2002. Early specification of the hierarchical organization of visual cortical areas in the macaque monkey. *Cerebral Cortex* 12: 453 – 465.

Batchelor, J., Harvery, A.G., Bryant, R.A. 1995. Stroop Color Word Test as a measure of attentional deficit following mild head injury. *The Clinical Neuropsychologist* 9: 180 – 186.

Baum, A.E., Akula, N., Cabanero, M., Cardona, I., Corona, W., Klemens, B., Schulze, T.G., Cichon, S., Rietschel, M., Nöthen, M.M., Georgi, A., Schumacher, J., Schwarz, M., Abou Jamra, R., Höfels, S., Propping, P., Satagopan, J., Detera-Wadleigh, S.D., Hardy, J., McMahon, F.J. 2008. A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Molecular Psychiatry* 13 (2): 197 - 207.

Beauregard, M., Leroux, J.-M., Bergman, S., Arzoumanian, S., Beaudoin, G., Bourgouin, P., Stip, E. 1998. The functional neuroanatomy of major depression: an fMRI study using an emotional activation paradigm. *NeuroReport* 9: 3253 – 3258.

Beauregard, M., Lévesque, J., Bourgouin, P. 2001. Neural correlates of conscious self-regulation of emotion. *The Journal of Neuroscience* 21 (18): RC165.

Bechara, A., Damasio, H., Tranel, D., Anderson, S.W. 1998. Dissociation of working memory from decision making within the human prefrontal cortex. *Journal of Neuroscience* 18 (1): 428 – 437.

Bechara, A., Tranel, D., Damasio, H. 2002. The somatic marker hypothesis and decision making. In: Boller, F. and Grafman, J. (eds.) *Handbook of Neuropsychology: Frontal Lobes*, vol. 7, 2nd ed. Amsterdam: Elsevier pp.117 – 143.

Bechara, A. 2004. The role of emotion in decision-making: evidence from neurological patients with orbitofrontal damage. *Brain and Cognition* 55: 30 – 40.

Beckstead, R.M., Morse, J.R., Norgren, R. 1980. The nucleus of the solitary tract in the monkey: projections to the thalamus and brain stem nuclei. *Journal of Comparative Neurology* 190 (2): 259 – 282.

Beer, J.S., Heerey, E.A., Keltner, D., Scabini, D., Knight, R.T. 2003. The regulatory function of self-conscious emotion: Insights from patients with orbitofrontal damage. *Journal of Personality and Social Psychology* 85: 594 – 604.

Beer, J.S., Knight, R.T., D'Esposito, M. 2006. Controlling the integration of emotion and cognition: The role of frontal cortex in distinguishing helpful from hurtful emotional information. *Psychological Science* 17: 448 – 453.

Bender, R., Lange, S. 2001. Adjusting for multiple testing--when and how? *Journal of Clinical Epidemiology* 54 (4): 343 - 349.

Benedetti, F., Dallaspezia, S., Colombo, C., Lorenzi, C., Pirovano, A., Smeraldi, E. 2010. Association between catechol-O-methyltransferase Val(108/158)Met polymorphism and psychotic features of bipolar disorder. *Journal of Affective Disorders* 125 (1 – 3): 341 – 344.

Benedetti, F., Dallaspezia, S., Locatelli, C., Radaelli, D., Poletti, S., Lorenzi, C., Pirovano, A., Colombo, C., Smeraldi, E. 2011. Recurrence of bipolar mania is associated with catechol-O-methyltransferase Val(108/158)Met polymorphism. *Journal of Affective Disorders* 132 (1 – 2): 293 – 296.

Benes, F.M., Bird, E.D. 1987. An analysis of the arrangement of neurons in the cingulate cortex of schizophrenic patients. *Archives of General Psychiatry* 44 (7): 608 – 616.

Benes, F.M., Davidson, J., Bird, E.D. 1986. Quantitative cytoarchitectoral studies of the cerebral cortex of schizophrenia. *Archives of General Psychiatry* 43 (1): 31 – 35.

Benes, F.M. 1991. Evidence for neurodevelopment disturbances in anterior cingulate cortex of post-mortem schizophrenic brain. *Schizophrenia Research* 5 (3): 187 – 188.

Benes, F.M. 1993. Neurobiological investigations in cingulate cortex of schizophrenic brain. *Schizophrenia Bulletin* 19 (3): 537 – 549.

Benes, F.M., Todtenkopf, M.S., Logiotatos, P., Williams, M. 2000. Glutamate decarboxylase(65)-immunoreactive terminals in cingulate and prefrontal cortices of schizophrenic and bipolar brain. *Journal of Clincal Neuroanatomy* 20 (3-4): 259 – 269.

Benes, F.M., Vincent, S.L., Todtenkopf, M. 2001. The density of pyramidal and nonpyramidal neurons in anterior cingulate cortex of schizophrenic and bipolar subjects. *Biological Psychiatry* 50 (6): 395 – 406.

Berrettini, W. 2002. Review of bipolar molecular linkage and association studies. *Current Psychiatry Reports* 4 (2): 124 – 129.

Bilder, R.M., Wu, H., Bogerts, B., Degreef, G., Ashtari, M., Alvir, J.M., Snyder, P.J., Lieberman, J.A. 1994. Absence of regional hemispheric volume asymmetries in first-episodeschizophrenia. *American Journal of Psychiatry* 151 (10): 1437 – 1447.

Biver, F., Goldman, S., Delvenne, V., Luxen, A., De Maertelaer, V., Hubain, P., Mendlewicz, J., Lotstra, F. 1994. Frontal and parietal metabolic disturbances in unipolar depression. *Biological Psychiatry* 36 (6): 381 – 388.

Black, D.N., Stip, E., Bedard, M., Kabay, M., Paquette, I., Bigras, M.J. 2000. Leukotomy revisited: late cognitive and behavioural effects in chronic institutionalized schizophrenics. *Schizophrenia Research* 43 (1): 57 – 64.

Blackwood, D.H., Pickard, B.J., Thomson, P.A., Evans, K.L., Porteous, D.J., Muir, W.J. 2007. Are some genetic risk factors common to schizophrenia, bipolar disorder and depression? Evidence from DISC1, GRIK4 and NRG1. *Neurotoxicity Research* 11 (1): 73 - 83.

Blair, R.J. 1995. A cognitive developmental approach to mortality: investigating the psychopath. *Cognition* 57 (1): 1 - 29.

Blair, R.J.R., Cipolotti, L. 2000. Impaired social response reversal: A case of 'acquired sociopathy'. *Brain* 123: 1122 – 1141.

Blair, R.J. 2001. Neurocognitive models of aggression, the antisocial personality disorders, and psychopathy. *Journal of Neurology, Neurosurgery and Psychiatry* 71 (6): 727 - 731.

Bleecker, M.L., Bolla-Wilson, K., Agnew, J., Meyers, D.A. 1988. Age-related sex differences in verbal memory. *The Journal of Clinical Psychology* 44: 403 – 411.

Bleuler, E. 1911. *Dementia Praecox oder die Gruppe der Schizophrenien*. Leipzig: Deuticke.

Bleuler, E. 1950. Dementia Praecox or the Group of Schizophrenias (J. Zinkin, Trans.). International Universities Press, New York (Original work published 1911).

Bloom, P.A., Fischler, I. 1980. Completion norms for 329 sentence contexts. *Memory and Cognition* 8 (6): 631 - 642.

Blumberg, H.P., Stern, E., Ricketts, S., Martinez, D., de Asis, J., White, T., Epstein, J., Isenberg, N., McBride, P.A., Kemperman, I., Emmerich, S., Dhawan, V., Eidelberg, D., Kocsis, J.H., Silbersweig, D.A. 1999. Rostral and orbital prefrontal cortex dysfunction in the manic state of bipolar disorder. *American Journal of Psychiatry* 156: 1986 – 1988.

Bora, E., Yucel, M., Fornito, A., Berk, M., Pantelis, C. 2008. Major psychoses with mixed psychotic and mood symptoms: are mixed psychoses associated with different neurobiological markers? *Acta Psychiatrica Scandinavica* 118 (3): 172 - 187.

Borgwardt, S.J., McGuire, P.K., Aston, J., Gschwandtner, U., Pflüger, M.O., Stieglitz, R.D., Radue, E.W., Riecher-Rossler, A. 2008. Reductions in frontal, temporal and parietal volume associated with the onset of psychosis. *Schizophrenia Research* 106: 108 – 114.

Borra, E., Ichinohe, N., Sato, T., Tanifuji, M., Rockland, K. 2009. Cortical connections to area TE in monkey: hybrid modular and distributed organization. *Cerebral Cortex* 20 (2): 257 – 270.

Bortolato, M., Pivac, N., Seler, D.M., Perkovic, M.N., Pessia, M., Di Giovanni, G. 2013. The role of the serotonergic system at the interface of aggression and suicide. *Neuroscience* 236**:** 160 – 185**.**

Bouras, C., Kövari, E., Hof, P.R., Riederer, B.M., Giannakopoulos, P. 2001. Anterior cingulate cortex pathology in schizophrenia and bipolar disorder. *Acta Neuropathologica* 102: 373 – 379.

Brambilla, P., Cerruti, S., Bellani, M., Perlini, C., Ferro, A., Marinelli, V., Giusto, D., Tomelleri, L., Rambaldelli, G., Tansella, M., Diwadkar, V.A. 2011. Shared impairment in associative learning in schizophrenia and bipolar disorder. *Progress in Neuropsychopharmacology and Biological Psychiatry* 35 (4): 1093 - 1099.

Bramham, J., Morris, R.G., Hornak, J., Bullock, P., Polkey, C.E. 2009. Social and emotional functioning following bilateral and unilateral neurosurgical prefrontal cortex lesions. *Journal of Neuropsychology* 3: 125 – 143.

Bremner, J.D., Innis, R.B., Salomon, R.M., Staib, L.H., Ng, C.K., Miller, H.L., Bronen, R.A., Krystal, J.H., Duncan, J., Rich, D., Price, L.H., Malison, R., Dey, H., Soufer, R., Charney, D.S. 1997. Positron emission tomography measurement of cerebral metabolic correlates of tryptophan depletion - induced depressive relapse. *Archives of General Psychiatry* 54 (4): 364 – 374.

Bremner, J.D., Vythilingam, M., Vermetten, E., Nazeer, A., Adil, J., Khan, S., Staib, L.H., Charney, D.S. 2002. Reduced volume of orbitofrontal cortex in major depression. *Biological Psychiatry* 51 (4): 273 – 279.

Brody, A.L., Saxena, S., Silverman, D.H., Alborzian, S., Fairbanks, L.A., Phelps, M.E., Huang, S.C., Wu, H.M., Maidment, K., Baxter, L.R. Jr. 1999. Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. *Psychiatry Research* 91: 127 – 139.

Broe, M., Hodges, J.R., Schofield, E., Shepherd, C.E., Kril, J.J., Halliday, G.M. 2003. Staging disease severity in pathologically confirmed cases of frontotemporal dementia. *Neurology* 60 (6): 1005 – 1011.

Broome, M.R., Matthiasson, P., Fusar-Poli, P., Woolley, J.B., Johns, L.C., Tabraham, P., Bramon, E., Valmaggia, L., Williams, S.C., Brammer, M.J., Chitnis, X., McGuire, P.K. 2009. Neural correlates of executive function and working memory in the 'at-risk mental state'. *The British Journal of Psychiatry* 194 (1): 25 - 33.

Broyd, S.J., Demanuele, C., Debener, S., Helps, S.K., James, C.J., Sonuga-Barke, E.J.S. 2009. Default-mode brain dysfunction in mental disorders: a systematic review. *Neuroscience and Biobehavioral Reviews* 33: 279 – 296.

Brutkowski, S., Davrowska, J. 1963. Disinhibition after prefrontal lesions as a function of duration of intertrial intervals. *Science* 139: 505 – 506.

Bunke, H., Riesen, K. 2011. Recent advances in graph-based pattern recognition with applications in document analysis. *Pattern Recognition* 44: 1057 – 1067.

Burdick, K.E., Hodgkinson, C.A., Szeszko, P.R., Lencz, T., Ekholm, J.M., Kane, J.M., Goldman, D., Malhotra, A.K. 2005. DISC1 and neurocognitive function in schizophrenia. *NeuroReport* 16: 1399 – 1402.

Burg, J.S., Burright, R.G., Donovick, P.J. 1995. Performance data for traumatic brain-injured subjects on the Gordon Diagnostic System (GDS) tests of attention. *Brain Injury* 9: 395 – 403.

Bush, G., Luu, P., Posner, M.I. 2000. Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences* 4: 215 – 222.

Butters, N., Butter, C., Rosen, J., Stein, D. 1973. Behavioyral effects of sequential and one-stageablations of orbital prefrontal cortex in the monkey. Experimental Neurology 39: 204 – 214.

Butti, C., Santos, M., Uppal, N., Hof, P.R. 2013. Von Economo neurons: Clinical and evolutionary perspectives. *Cortex* 49 (1): 312 – 326.

Byrne, M., Hodges, A., Grant, E., Owens, D.C., Johnstone, E.C. 1999. Neuropsychological assessment of young people at high genetic risk for developing schizophrenia compared with controls: preliminary findings of the Edinburgh High Risk Study (EHRS). *Psychological Medicine* 29: 1161 - 1173.

C

Cabeza, R., Nyberg, L. 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience* 12: 1 – 47.

Cachia, A., Mangin, J.-F., Rivière, D., Papadopoulos-Orfanos, D., Kherif, F., Bloch, I., Régis, J. 2003. A generic framework for the parcellation of the cortical surface into gyri using geodesic Voronoï diagrams. *Medical Image Analysis* 7 (4): 403 – 416.

Calaminus, C., Hauber, W. 2008. Guidance of instrumental behavior under reversal conditions requires dopamine D1 and D2 receptor activation in the orbitofrontal cortex. *Neuroscience* 154 (4): 1195 – 1204.

Callicott, J.H., Straub, R.E., Pezawas, L., Egan, M.F., Mattay, V.S., Hariri, A.R., Verchinski, B.A., Meyer-Lindenberg, A., Balkissoon, R., Kolachana, B., Goldberg, T.E., Weinberger, D.R. 2005. Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. *Proceeding of the National Academy of Science USA.* 102 (24): 8627 - 8632.

Cannon, M., Jones, P., Gilvarry, C., Rifkin, L., McKenzie, K., Foerster, A., Murray, R.M. 1997. Premorbid social functioning in schizophrenia and bipolar disorder: similarities and differences. *American Journal of Psychiatry* 154 (11): 1544 - 1550.

Cannon, T.D., Hennah, W., van Erp, T.G.M., Thompson, P.M., Lonnqvist, J., Huttunen, M., Gasperoni, T., Tuulio-Henriksson, A., Pirkola, T., Toga, A.W., Kaprio, J., Mazziotta, J., Peltonen, L. 2005. Association of DISC1/TRAX haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short- and long-term memory. *Archives of General Psychiatry* 62 (11): 1205 – 1213.

Carmichael, S.T., Price, J.L. 1994. Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. *The Journal of Comparative Neurology* 346: 366 – 402.

Carmichael, S.T., Price, J.L. 1995 a. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *The Journal of Comparative Neurology* 363: 615 – 641.

Carmichael, S.T., Price, J.L. 1995 b. Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. *The Journal of Comparative Neurology* 363: 642 – 664.

Carmichael, S.T., Price, J.L. 1996. Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *The Journal of Comparative Neurology* 371 (2): 179 – 207.

Carroll, B.J., Feinberg, M., Greden, J.F., Tarika, J., Albala, A.A., Haskett, R.F., James, N.M., Kronfol, Z., Lohr, N., Steiner, M., de Vigne, J.P., Young, E. 1981. A specific laboratory test for the diagnosis of melancholia. Standardization, validation, and clinical utility. *Archives of General Psychiatry* 38 (1): 15 – 22.

Catalano, M. 2001. Functionally gene-linked polymorphic regions and genetically controlled neurotransmitters metabolism. *European Neuropsychopharmacology* 11: 431 - 439.

Catapano, L.A., Manji, H.K. 2007. G protein-coupled receptors in major psychiatric disorders. *Biochimica et Biophysica Acta* 1768: 976 – 993.

Cavada, C., Company, T., Tejedor, J., Cruz Rizzolo, R.J., Reinoso Suarez, F. 2000. The anatomical connections of the macaque monkey orbitofrontal cortex: a review. *Cerebral Cortex* 10: 220 – 242.

Cerasa, A., Cherubini, A., Quattrone, A., Gioia, M.C., Magariello, A., Muglia, M., Manna, I., Assogna, F., Caltagirone, C., Spalletta, G. 2010. Morphological correlates of MAO A VNTR polymorphism: new evidence from cortical thickness measurement. *Behavioural Brain Research* 211: 118 – 124.

Cerasa, A., Quattrone, A., Gioia, M.C., Tarantino, P., Annesi, G., Assogna, F., Caltagirone, C., De Luca, V., Spalletta, G. 2011. Dysbindin C–A–T

haplotype is associated with thicker medial orbitofrontal cortex in healthy population. *NeuroImage* 55: 508 – 513.

Cerullo, M.A., Adler, C.M., Delbello, M.P., Strakowski, S.M. 2009. The functional neuroanatomy of bipolar disorder. *International Review of Psychiatry* 21: 314 – 322.

Chaddock, C.A., Barker, G.J., Marshall, N., Schulze, K., Hall, M.H., Fern, A., Walshe, M., Bramon, E., Chitnis, X.A., Murray, R., McDonald, C. 2009. White matter microstructural impairments and genetic liability to familial bipolar I disorder. *The British Journal of Psychiatry* 194 (6): 527 – 534.

Chakirova, G., Welch, K.A., Moorhead, T.W.J., Stanfield, A.C., Hall, J., Skehel, P., Brown, V.J., Johnstone, E.C., Owens, D.G.C., Lawrie, S.M., McIntosh, A.M. 2010. Orbitofrontal morphology in people at high risk of developing schizophrenia. *European Psychiatry* 25: 366 – 372.

Chakirova, G., Whalley, H.C., Thomson, P.A., Hennah, W., Moorhead, T.W., Welch, K.A., Giles, S., Hall, J., Johnstone, E.C., Lawrie, S.M., Porteous, D.J., Brown, V.J., McIntosh, A.M. 2011. The effects of DISC1 risk variants on brain activation in controls, patients with bipolar disorder and patients with schizophrenia. *Psychiatry Research* 192 (1): 20 - 28.

Chi, J.G., Dooling, E.C., Gilles, F.H. 1977. Gyral development of the human brain. *Annals of Neurology* 1: 86 – 93.

Chiavaras, M.M., Petrides M. 2000. Orbitofrontal sulci of the human and macaque monkey brain. *The Journal of Comparative Neurology* 422: 35 – 54.

Chowdari, K.V., Mirnics, K., Semwal, P., Wood, J., Lawrence, E., Bhatia, T., Deshpande, S.N., Thelma, B.K., Ferrell, R.E., Middleton, F.A., Devlin, B., Levitt, P., Lewis, D.A., Nimgaonkar, V.L. 2002. Association and linkage analyses of RGS4 polymorphisms in schizophrenia. *Human Molecular Genetics* 11: 1373 – 1380.

Chua, S.E., Wright, I.C., Poline, J.B., Liddle, P.F., Murray, R.M., Frackowiak, R.S., Friston, K.J., McGuire, P.K. 1997. Grey matter correlates of syndromes in schizophrenia. A semi-automated analysis of structural magnetic resonance images. *The British Journal of Psychiatry* 170: 406 – 410.

Chumakov, I., Blumenfeld, M., Guerassimenko, O., Cavarec, L., Palicio, M., Abderrahim, H., Bougueleret, L., Barry, C., Tanaka, H., La Rosa, P., Puech, A., Tahri, N., Cohen-Akenine, A., Delabrosse, S., Lissarrague, S., Picard, F.P., Maurice, K., Essioux, L., Millasseau, P., Grel, P., Debailleul, V., Simon, A.M., Caterina, D., Dufaure, I., Malekzadeh, K., Belova, M., Luan, J.J., Bouillot, M., Sambucy, J.L., Primas, G., Saumier, M., Boubkiri, N., Martin-Saumier, S., Nasroune, M., Peixoto, H., Delaye, A., Pinchot, V., Bastucci, M.,

Guillou, S., Chevillon, M., Sainz-Fuertes, R., Meguenni, S., Aurich-Costa, J., Cherif, D., Gimalac, A., Van Duijn, C., Gauvreau, D., Ouellette, G., Fortier, I., Raelson, J., Sherbatich, T., Riazanskaia, N., Rogaev, E., Raeymaekers, P., Aerssens, J., Konings, F., Luyten, W., Macciardi, F., Sham, P.C., Straub, R.E., Weinberger, D.R., Cohen, N., Cohen, D. 2002. Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* 99 (21): 13675 – 13680.

Clarke, H.F., Walker, S.C., Dalley, J.W., Robbins, T.W., Roberts, A.C. 2007. Cognitive inflexibility after prefrontal serotonin depletion is behaviourally and neurochemically specific. Cerebral Cortex 17: 18 – 27.

Cohen, R.M., Gross, M., Nordahl, T.E., Semple, W.E., Oren, D.A., Rosenthal, N. 1992. Preliminary data on the metabolic brain pattern of patients with winter seasonal affective disorder. *Archives of General Psychiatry* 49: 545 – 552.

Corfas, G., Roy, K., Buxbaum, J.D. 2004. Neuregulin 1–erbB signaling and the molecular/cellular basis of schizophrenia. *Nature Neuroscience* 7 (6): 575 – 580.

Cosway, R., Byrne, M., Clafferty, R., Hodges, A., Grant, E., Abukmeil, S.S., Lawrie, S.M., Miller, P., Johnstone, E. C. 2000. Neuropsychological change in young people at high risk for schizophrenia: results from the first two neuropsychological assessments of the Edinburgh High Risk Study. *Psychological Medicine* 30: 1111 - 1121.

Cotter, D., Landau, S., Beasley, C., Stevenson, R., Chana, G., MacMillan, L., Everall, I. 2002. The density and spatial distribution of GABAergic neurons, labelled using calcium binding proteins, in the anterior cingulate cortex in major depressive disorder, bipolar disorder, and schizophrenia. *Biological Psychiatry* 51 (5): 377 – 386.

Cotter, D., Hudson, L., Landau, S. 2005. Evidence for orbitofrontal pathology in bipolar disorder and major depression, but not in schizophrenia. *Bipolar Disorders* 7: 358 – 369.

Coyle J.T. Glutamate and schizophrenia: beyond the dopamine hypothesis. 2006. *Cellular and Molecular Neurobiology* 26: 365 – 384.

Crawford, J.R., Parker, D.M., Stewart, L.E., Besson, J.A.O., De Lacey, G. 1989. Prediction of WAIS IQ with the National Adult Reading Test: Cross-validation and extension. *British Journal of Clinical Psychology* 28: 267 – 273.

Crespo-Facorro, B., Kim, J.J., Andreasen, N.C., O'Leary, D.S., Wiser, A.K., Bailey, J.M., Harris, G., Magnotta, V.A. 1999. Human frontal cortex: an MRI-based parcellation method. *Neuroimage* 10 (5): 500 – 519.

Creutzfeldt, O.D. 1995. Cortex cerebri: performance, structural and functional organization of the cortex. Oxford: Oxford UP.

Crosson, B., Sadek, J.R., Bobholz, J.A., Gokcay, D., Mohr, C.M., Leonard, C.M., Maron, L., Auerbach, E.J., Browd, S.R., Freeman, A.J., Briggs, R.W. 1999. Activity in the paracingulate and cingulate sulci during word generation: an fMRI study of functional anatomy. *Cerebral Cortex* 9 (4): 307 - 316.

Curry, C.J., Stevenson, R.E., Aughton, D., Byrne, J., Carey, J.C., Cassidy, S., Cunniff, C., Graham, J.M.Jr, Jones, M.C., Kaback, M.M., Moeschler, J., Schaefer, G.B., Schwartz, S., Tarleton, J., Opitz, J. 1997. Evaluation of mental retardation: recommendations of a consensus conference: American College of Medical Genetics. *American Journal of Medical Genetics* 72 (4): 468 – 477.

Curtis, V.A., Dixon, T.A., Morris, R.G., Bullmore, E.T., Brammer, M.J., Williams, S.C.R., Sharma, T., Murray, R.M., McGuire, P.K. 2001. Differential frontal activation in schizophrenia and bipolar illness during verbal fluency. *Journal of Affective Disorders* 66: 111 – 121.

Curtis, V.A., Thompson, J.M., Seal, M.L., Monks, P.J., Lloyd, A.J., Harrison, L., Brammer, M.J., Williams, S.C., Murray, R.M., Young, A.H., Ferrier, I.N. 2007. The nature of abnormal language processing in euthymic bipolar I disorder: Evidence for a relationship between task demand and prefrontal function. *Bipolar Disorder* 9 (4): 358 – 369.

D

Dale, A.M., Fischl, B., Sereno, M.I. 1999. Cortical surface-based analysis I. Segmentation and surface reconstruction. *NeuroImage* 9: 179 – 194.

Dalley, J.W., Roiser, J.P. 2012. Dopamine, serotonin and impulsivity. *Neuroscience* 215: 42 – 58.

Damasio, A.R., Tranel, D., Damasio, H. 1990. Individuals with sociopathic behaviour caused by frontal damage fail to respond autonomically to social stimuli. *Behavioural Brain Research* 41: 81 – 94.

Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L., Parvizi, J., Hichwa, R.D. 2000. Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neuroscience* 3 (10): 1049 – 1056.

Das Gupta, R., Guest, J.F. 2002. Annual cost of bipolar disorder to UK Society. *The British Journal of Psychiatry* 180: 227 - 233.

Dawson, G., Munson, J., Estes, A., Osterling, J., McPartland, J., Toth, K., Carver, L., Abbott, R. 2002. Neurocognitive function and joint attention ability in young children with autism spectrum disorder versus developmental delay. *Child Development* 73: 345 – 358.

De Aguiar Ferreira, A., Neves, F.S., Pimenta, G.J.G.S., Mello, M.P., Miranda, D.M., Romano-Silva, M.A., De Marco, L.A., Corrêa, H. 2010. The role of genetic variation of BDNF gene in antidepressant-induced mania in bipolar disorder. *Psychiatry Research* 180 (1): 54 – 56.

De Almeida, J., Mengod, G. 2010. D2 and D4 dopamine receptor mRNA distribution in pyramidal neurons and GABAergic subpopulations in monkey prefrontal cortex: implications for schizophrenia treatment. *Neuroscience* 170 (4): 1133 – 1139.

Depp, C.A., Moore, D.J., Sitzer, D., Palmer, B.W., Eyler, L.T., Roesch, S., Lebowitz, B.D., Jeste, D.V. 2007. Neurocognitive impairment in middle-aged and older adults with bipolar disorder: comparison to schizophrenia and normal comparison subjects. *Journal of Affective Disorders* 101 (1- 3): 201 – 209.

DeRosse, P., Hodgkinson, C.A., Lencz, T., Burdick, K.E., Kane, J.M., Goldman, D., Malhotra, A.K. 2007. Disrupted in schizophrenia 1 genotype and positive symptoms in schizophrenia. *Biological Psychiatry* 61 (10): 1208 - 1210.

De Wall, C., Wilson, B.A., Baddeley, A.D. 1994. The Extended Rivermead Behavioural Memory Test: a measure of everyday memory performance in normal adults. *Memory* 2 (2): 149 – 166.

Dias, R., Robbins, T.W., Roberts, A.C. 1996. Dissociation in prefrontal cortex of affective and attentional shifts. *Nature* 380: 69 – 72.

Ding, L., Hegde, A.N. 2009. Expression of RGS4 Splice Variants in Dorsolateral Prefrontal Cortex of Schizophrenic and Bipolar Disorder Patients. *Biological Psychiatry* 65 (6): 541 – 545.

Dixon, T., Kravariti, E., Frith, C., Murray, R.M., McGuire, P.K. 2004. Effect of symptoms on executive function in bipolar illness. *Psychological Medicine* 34: 811 – 821.

Dombrowski, S.M., Hilgetag, C.C., Barbas, H. 2001. Quantitative architecture distinguishes prefrontal cortical systems in the rhesus monkey. *Cerebral Cortex* 11 (10): 975 - 988.

Dougherty, D.D., Shin, L.M., Alpert, N.M., Pitman, R.K., Orr, S.P., Lasko, M., Macklin, M.L., Fischman, A.J., Rauch, S.L. 1999. Anger in healthy men: a PET study using script-driven imagery. *Biological Psychiatry* 46: 466 – 472.

Drevets, W.C., Ongur, D., Price, J.L. 1998. Neuroimaging abnormalities in the subgenual prefrontal cortex: Implications for the pathophysiology of familial mood disorders. *Molecular Psychiatry* 3: 220 – 226.

Drevets, W.C. 2001. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Current Opinion in Neurobiology* 11 (2): 240 – 249.

Duvernoy, H. 1991. *The Human Brain: Surface, Three-Dimensional Sectional Anatomy and MRI.* Springer-Verlag, Wien.

E

Eastwood, S.L., Harrison, P.J. 2001. Synaptic pathology in the anterior cingulate cortex in schizophrenia and mood disorders. A review and a Western blot study of synaptophysin, GAP-43 and the complexins. *Brain Research Bulletin* 55 (5): 569 – 578.

Eblen, F., Graybiel, A.M. 1995. Highly restricted origin of prefrontal cortical inputs to striosomes in the macaque monkey. *The Journal of Neuroscience* 15: 5999 – 6013.

Egan, M.F., Goldberg, T.E., Kolachana, B.S., Callicott, J.H., Mazzanti, C.M., Straub, R.E., Goldman, D., Weinberger, D.R. 2001. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* 98 (12): 6917 – 6922.

Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., Weinberger, D.R. 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 112 (2): 257 – 269.

Endicott, J., Spitzer, R.L. 1978. A diagnostic interview: the schedule for affective disorder and schizophrenia. *Archives of General Psychiatry* 35 (7): 837 – 844.

Everitt, B.J., Robbins, T.W. 1997. Central cholinergic systems and cognition. *Annual Review of Psychology* 48: 649 - 684.

F

Fahim, C., Stip, E., Mancini-Marïe, A., Mensour, B., Boulay, L.J., Leroux, J.M., Beaudoin, G., Bourgouin, P., Beauregard, M. 2005. Brain activity during emotionally negative pictures in schizophrenia with and without flat affect: An fMRI study. *Psychiatry Research* 140 (1): 1 - 15.

Fallgatter, A.J., Ehlis, A.C., Herrmann, M.J., Hohoff, C., Reif, A., Freitag, C.M., Deckert, J. 2010. DTNBP1 (dysbindin) gene variants modulate prefrontal brain function in schizophrenic patients support for the glutamate hypothesis of schizophrenias. *Genes, Brain and Behavior* 9(5): 489 - 497.

Fellows, L.K., Farah, M.J. 2005. Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans. *Cerebral Cortex* 15: 58 – 63.

Fernandes, B.S., Gama, C.S., Ceresér, K.M., Yatham, L.N., Fries, G.R., Colpo, G., de Lucena, D., Kunz, M., Gomes, F.A., Kapczinski, F. 2011. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: A systematic review and meta-regression analysis. *Journal of Psychiatric Research* 45 (8): 995 – 1004.

Fernandez-Duque, D., Posner, M.I. 2001. Brain imaging of attentional networks in normal and pathological states. *Journal of Clinical and Experimental Neuropsychology* 23: 74 – 93.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W. 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition. (SCID-I/NP) New York: Biometrics Research, New York State Psychiatric Institute.

Fischer, B.A., Carpenter Jr., W.T. 2009. Will the Kraepelinian dichotomy survive DSM-V? *Neuropsychopharmacology* 34: 2081 – 2087.

Fischl, B., Sereno, M.I., Dale, A.M. 1999 a. Cortical surface-based analysis II: inflation, flattening, and a surface-based coordinate system. *NeuroImage* 9: 195 – 207.

Fischl, B., Sereno, M.I., Tootell, R.B.H., Dale, A.M. 1999 b. High resolution intersubject averaging and a coordinate system for the cortical surface. *Human Brain Mapping* 8 (4): 272 – 284.

Fischl, B., Dale, A.M. 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America* 97: 11050 – 11055.

Fornito, A., Yücel, M., Wood, S.J., Stuart, G.W., Buchanan, J.-A., Proffitt, T., Anderson, V., Velakoulis, D., Pantelis, C. 2004. Individual differences in anterior cingulate/paracingulate morphology are related to executive functions in healthy males. *Cerebral Cortex* 14: 424 – 431.

Fornito, A., Whittle, S., Wood, S., Velakoulis, D., Pantelis, C., Yücel, M. 2006. The influence of sulcal variability on morphometry of the human anterior cingulate and paracingulate cortex. *Neuroimage.* 33: 843 - 854.

Fornito, A., Malhi, G.S., Lagopoulos, J., Ivanovski, B., Wood, S.J., Velakoulis, D., Saling, M.M., McGorry, P.D., Pantelis, C., Yucel, M. 2007. In vivo evidence for early neurodevelopmental anomaly of the anterior cingulate cortex in bipolar disorder. *Acta Psychiatrica Scandinavica* 116: 467 – 472.

Fornito, A., Malhic, G.S., Lagopoulos, J., Ivanovski, B., Wood, S.J., Saling, M.M., Pantelis, C., Yücel, M. 2008. Anatomical abnormalities of the anterior cingulate and paracingulate cortex in patients with bipolar I disorder. *Psychiatry Research: Neuroimaging* 162: 123 – 132.

Franceshsi, M., Anchisi, D., Pelati, O., Zuffi, M., Matarrese, M., Moresco, R.M., Fazio, F., Perani, D. 2005. Glucose metabolism and serotonin receptors in the frontotemporal lobe degeneration. *Annals of Neurology* 57 (2): 216 – 225.

Frangou, S., Chitins, X., Williams, S.C.R. 2004. Mapping IQ and gray matter density in healthy young people. *NeuroImage*. 23: 800 – 805.

Frazier, J.A., Breeze, J.L., Papadimitriou, G., Kennedy, D.N., Hodge, S.M., Moore, C.M., Howard, J.D., Rohan, M.P., Caviness, V.S., Makris, N. 2007. White matter abnormalities in children with and at risk for bipolar disorder. *Bipolar Disorder* 9: 799 – 809.

Fredrikson, M., Fischer, H., Wik, G., 1997. Central blood flow during anxiety provocation. *Journal of Clinical Psychiatry* 58: 1616 – 1621.

Freedman, M. 1990. Object alternation and orbitofrontal system dysfunction in Alzheimer's and Parkinson's disease. *Brain and Cognition* 14 (2): 134 - 143.

Freedman, L.J., Insel, T.R., Smith, Y. 2000. Subcortical projections of area 25 (subgenual cortex) of the macaque monkey. *The Journal of Comparative Neurology* 421 (2): 172 – 188.

Fujiwara, J., Tobler, P.N., Taira, M., Iijima, T., Tsutsui, K. 2008. Personality-dependent dissociation of absolute and relative loss processing in orbitofrontal cortex. *European Journal of Neuroscience.* 27: 1547 – 1552.

Fuster, J.M. 1989. The Prefrontal Cortex. New York: Raven Press.

G

Gabbott, P.L.A., Warner, T.A., Jays, P.R.L., Salway, P., Busby, S.J. 2005. Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. *The Journal of Comparative Neurology* 492 (2): 145 – 177.

Gallagher, H.L., Frith, C.D. 2003. Functional imaging of 'Theory of Mind'. *Trends in Cognitive Sciences* 7 (2): 77 – 83.

Gaser, C., Volz, H.P., Kiebel, S., Riehemann, S., Sauer, H. 1999. Detecting structural changes in whole brain based on non-linear deformations-application to schizophrenia research. *Neuroimage* 10 (2): 107 – 113.

George, M.S., Ketter, T.A., Parekh, P.I., Horwitz, B., Herscovitch, P., Post, R.M. 1995. Brain activity during transient sadness and happiness in healthy women. *American Journal of Psychiatry* 152: 341 – 351.

Gilbert, C.D., Sigman, M. 2007. Brain states: top-down influences in sensory processing. *Neuron* 54 (5): 677 - 696.

Girgis, R.R., Minshew, N.J., Melhem, N.M., Nutche, J.J., Keshavan, M.S., Hardan, A.Y. 2007. Volumetric alterations of the orbitofrontal cortex in autism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 31 (1): 41 – 45.

Glahn, D.C., Laird, A.R., Ellison-Wright, I., Thelen, S.M., Robinson, J.L., Lancaster, J.L., Bullmore, E., Fox, P.T. 2008. Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biological Psychiatry* 64 (9): 774 - 781.

Glatt, S.J., Faraone, S.V., Tsuang, M.T. 2003 a. Association between a functional catechol O-methyltransferase gene polymorphism and schizophrenia: meta-analysis of case-control and family-based studies. *The American Journal of Psychiatry* 160 (3): 469 – 476.

Glatt, S.J., Faraone, S.V., Tsuang, M.T. 2003 b. Meta-analysis identifies an association between the dopamine D2 receptor gene and schizophrenia. *Molecular Psychiatry* 8 (11): 911 – 915.

Goldberg, E. 2003. Attention and motivation. In Bloom, F. et al., editors. *The Dana guide to brain health,* Dana Press, pp. 196 - 199.

Goldberg, T.E., David, A., Gold, J.M. 2003. Neuropsychological deficit in schizophrenia. In Hirsch, S.R., Weinberger, D.R., editors. *Schizophrenia*, 2nd edition, Blackwell publishing company, Massachusetts, USA. Chapter 10.

Goldberg, E., Barr, W. 2003. Knowledge systems. In Byrne, J., editor. *Learning and memory,* 2nd ed., Macmillan Reference, pp. 306 - 309.

Golden, J.C. 1978. Stroop Color and Word Test. Stoelting: Chicago, IL.

Goldstein, J.M., Goodman, J.M., Seidman, L.J., Kennedy, D.N., Makris, N., Lee, H., Tourville, J., Caviness Jr., V.S., Faraone, S.V., Tsuang, M.T. 1999. Cortical abnormalities in schizophrenia identified by structural magnetic resonance imaging. *Archives of General Psychiatry* 56: 537 – 547.

Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N., Friston, K.J., Frackowiak, R.S. 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14 (1 Pt 1): 21 – 36.

Goodwin, F.K., Jamison, K.R. 2007. *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression, 2nd Edition*. New York: Oxford University Press.

Gottesman, I.I., Shields, J. 1976. A critical review of recent adoption, twin, and family studies of schizophrenia: behavioural genetics perspectives. *Schizophrenia Bulletin* 2 (3): 360 – 401.

Gottesman, I. 1991. Schizophrenia genesis: the origins of madness. Attkinson, R.C., Lindzey, G., Thompson, R.F., editors. New York: WH Freeman and company.

Gottfried, C., Riesgo, R. 2011. *Antipsychotics in the treatment of autism, autism spectrum disorders - from genes to environment*, Prof. Williams, T. (editor), ISBN: 978-953-307-558-7, InTech, Available from: http://www.intechopen.com/books/autism-spectrum-disorders-from-genes-toenvironment/antipsychotics-in-the-treatment-of-autism.

Grafman, J., Vance, S.C., Weingartner, H., Salazar, A.M., Amin, D. 1986. The effects of lateralized frontal lesions on mood regulation. *Brain* 109: 1127 – 1148.

Grafman, J., Schwab, K., Warden, D., Pridgen, A., Brown, H.R., Salazar, A.M. 1996. Frontal lobe injuries, violence, and aggression: a report of the Vietnam head injury study. *Neurology* 46: 1231 – 1238.

Grant, D.A., Berg, E.A. 1948. A behavioural analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. *Journal of Experimental Psychology* 38 (4): 404 – 411.

Gregory, C., Lough, S., Stone, V., Erzinclioglu, S., Martin, L., Baron-Cohen, S., Hodges, J.R. 2002. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain* 125 (4): 752 - 764.

Grigoroiu-Serbanescu, M., Herms, S., Diaconu, C.C., Jamra, R.A., Meier, S., Bleotu, C., Neagu, A.I., Prelipceanu, D., Sima, D., Gherghel, M., Mihailescu, R., Rietschel, M., Nöthen, M.M., Cichon, S., Mühleisen, T.W. 2010. Possible association of different G72/G30 SNPs with mood episodes and persecutory delusions in bipolar I Romanian patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 34 (4): 657 – 663.

Groman, S.M., James, A.S., Seu, E., Crawford, M.A., Harpster, S.N., Jentsch, J.D. 2013. Monoamine levels within the orbitofrontal cortex and putamen interact to predict reversal learning performance. *Biological Psychiatry* In press.

Gruber, O., Henseler, I., Scherk, H., Wobrock, T., Falkai, P. 2008. Unique and overlapping abnormalities in brain activation during verbal working memory task performance: a comparison between patients with schizophrenia and bipolar affective disorder. *Schizophrenia Research* 98: 3 – 199.

Guo, S., Tang, W., Shi, Y., Huang, K., Xi, Z., Xu, Y., Feng, G., He, L. 2006. RGS4 polymorphisms and risk of schizophrenia: An association study in Han Chinese plus meta-analysis. *Neuroscience Letters* 406 (1 – 2): 122 – 127.

Gur, R.E., Cowell, P.E., Latshaw, A., Turetsky, B.I., Grossman, R.I., Arnold, S.E., Bilker, W.B., Gur, R.C. 2000. Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Archives of General Psychiatry* 57 (8): 761 – 768.

Gurling, H.M.D., Critchley, H., Datta, S.R., McQuillin, A., Blaveri, E., Thirumalai, S., Pimm, J., Krasucki, R., Kalsi, G., Quested, D., Lawrence, J., Bass, N., Choudhury, K., Puri, V., O'Daly, O., Curtis, D., Blackwood, D., Muir, W., Malhotra, A.K., Buchanan, R.W., Good, C.D., Frackowiak, R.S.J., Dolan, R.J. 2006. Genetic association and brain morphology studies and the chromosome 8p22 pericentriolar material 1 (PCM1) gene in susceptibility to schizophrenia. *Archives of General Psychiatry* 63 (8): 844 – 854.

H

Hafner, H., Maurer, K., Loffler, W., Riecher-Rossler, A. 1993. The Influence of age and sex on the onset and early course of schizophrenia. *The British Journal of Psychiatry* 162: 80 – 86.

Hajek, T., Gunde, E., Slaney, C., Propper, L., MacQueen, G., Duffy, A., Alda, M. 2009. Striatal volumes in affected and unaffected relatives of bipolar patients: High-risk study. *Journal of Psychiatric Research* 43: 724 – 729.

Halperin, J.M., Wolf, I., Greenblatt, E.R., Young, G. 1991. Subtype analysis of commission errors on the continuous performance test in children. *Developmental Neuropsychology* 7: 207 – 217.

Hamilton, M. 1960. A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry.* 23: 56 – 62.

Hampshire, A., Owen, A.M. 2006. Fractionating Attentional Control Using Event - Related fMRI. *Cerebral Cortex* 16: 1679 – 1689.

Han, X., Jovicich, J., Salat, D., van der Kouwe, A., Quinn, B., Czanner, S., Busa, E., Pacheco, J., Albert, M., Killiany, R., Maguire, P., Rosas, D., Makris, N., Dale, A., Dickerson, B., Fischl, B. 2006. Reliability of MRI-derived measurements of human cerebral cortical thickness: The effects of field strength, scanner upgrade and manufacturer. *NeuroImage* 32 (1): 180 – 194.

Hanes, K.R., Andrewes, D.G., Smith, D.J., Pantelis, C. 1996. A brief assessment of executive control dysfunction: Discriminant validity and homogeneity of planning, set shift, and fluency measures. *Archives of Clinical Neuropsychology* 11: 185 - 191.

Harrow, M., Green, K.E., Sands, J.R., Jobe, T.H., Goldberg, J.F., Kaplan, K.J., Martin, E.M. 2000. Thought Disorder in Schizophrenia and Mania: Impaired Context. *Schizophrenia Bulletin* 26 (4): 879 – 891.

Harvey, I., Ron, M.A., Du Boulay, G., Wicks, D., Lewis, S.W., Murray, R.M. 1993. Reduction of cortical volume in schizophrenia on magnetic resonance imaging. *Psychological Medicine* 23 (3): 591 – 604.

Hashimoto, R., Numakawa, T., Ohnishi, T., Kumamaru, E., Yagasaki, Y., Ishimoto, T., Mori, T., Nemoto, K., Adachi, N., Izumi, A., Chiba, S., Noguchi, H., Suzuki, T., Iwata, N., Ozaki, N., Taguchi, T., Kamiya, A., Kosuga, A., Tatsumi, M., Kamijima, K., Weinberger, D.R., Sawa, A., Kunugi, H. 2006. Impact of the DISC1 Ser704Cys polymorphism on risk for major depression, brain morphology and ERK signaling. *Human Molecular Genetics.* 15 (20): 3024 - 3033.

Hasselmo, M.E., Sarter M. 2011. Modes and Models of Forebrain Cholinergic Neuromodulation of Cognition. *Neuropsychopharmacology* 36 (1): 52 – 73.

Hatzimanolis, A., Vitoratou, S., Mandelli, L., Vaiopoulos, C., Nearchou, F.A., Stefanis, C.N., Serretti, A., Stefanis, N.C. 2013. Potential role of membrane-

bound COMT gene polymorphisms in female depression vulnerability. *Journal of Affective Disorders* In Press, Corrected Proof.

Haxby, J.V. 2012. Multivariate pattern analysis of fMRI: The early beginnings. *NeuroImage* 62: 852 – 855.

Hayasaka, S., Phan, K.L., Liberzon, I., Worsley, K.J., Nichols, T.E. 2004. Nonstationary cluster - size inference with random field and permutation methods. *NeuroImage* 22: 676 - 687.

Heaton, R.K. 1981. *Wisconsin Card Sorting Test manual.* Odessa, FL: Psychological Assessment Resources.

Heberlein, A.S., Padon, A.A., Gillihan, S.J., Farah, M.J., Fellows, L.K. 2008. Ventromedial frontal lobe plays a critical role in facial emotion recognition. *Journal of Cognitive Neuroscience* 20: 721 – 733.

Heimer, L. 1972. The olfactory connections of the diencephalon in the rat. An experimental light- and electron-microscopic study with special emphasis on the problem of terminal degeneration. *Brain, Behavior and Evolution* 6 (1): 484 – 523.

Hennah, W., Varilo, T., Kestila, M., Paunio, T., Arajarvi, R., Haukka, J., Parker, A., Martin, R., Levitzky, S., Partonen, T., Meyer, J., Lönnqvist, J., Peltonen, L., Ekelund, J. 2003. Haplotype transmission analysis provides evidence of association for DISC1 to schizophrenia and suggests sex-dependent effects. *Human Molecular Genetics* 12 (23): 3151 - 3159.

Hennah, W., Thomson, P., McQuillin, A., Bass, N., Loukola, A., Anjorin, A., Blackwood, D., Curtis, D., Deary, I.J., Harris, S.E., Isometsä, E.T., Lawrence, J., Lönnqvist, J., Muir, W., Palotie, A., Partonen, T., Paunio, T., Pylkkö, E., Robinson, M., Soronen, P., Suominen, K., Suvisaari, J., Thirumalai, S., St Clair, D., Gurling, H., Peltonen, L., Porteous, D. 2009. DISC1 association, heterogeneity and interplay in schizophrenia and bipolar disorder. *Molecular Psychiatry* 14 (9): 865 - 873.

Himmelheber, A.M., Sarter, M., Bruno, J.P. 2001. The effects of manipulations of attentional demand on cortical acetylcholine release. *Cognitive brain research* 12 (3): 353 – 370.

Hodges, A., Byrne, M., Grant, E., Johnstone, E. 1999. People at risk of schizophrenia. Sample characteristics of the first 100 cases in the Edinburgh High - Risk Study. *British Journal of Psychiatry* 174: 547 - 553.

Hodgkinson, C.A., Goldman, D., Jaeger, J., Persaud, S., Kane, J.M., Lipsky, R.H., Malhotra, A.K. 2004. Disrupted in schizophrenia 1 (DISC1): association

with schizophrenia, schizoaffective disorder, and bipolar disorder. *The American Journal of Human Genetics* 75 (5): 862 - 872.

Holland, P.C., Gallagher, M. 2004. Amygdala - frontal interactions and reward expectancy. *Current Opinion in Neurobiology* 14: 148 – 155.

Holmes, A., Wrenn, C.C., Harris, A.P., Thayer, K.E., Crawley, J.N. 2002. Behavioral profiles of inbred strains on novel olfactory, spatial and emotional tests for reference memory in mice. *Genes, Brain, and Behavior* 1 (1): 55 – 69.

Holzbauer, M., Muscholl, E., Racké, K., Sharman, D.F. 1983 a. Evidence that dopamine is a neurotransmitter in the neurointermediate lobe of the hypophysis. *Progress in Brain Research* 60: 357 – 364.

Holzbauer, M., Racké, K., Muscholl, E., Sharman, D. 1983 b. Dopamine release and synthesis in the neurointermediate lobe of the rat hypophysis in vitro after electrical stimulation of the pituitary stalk. *Brain Research* 277 (1): 47 – 54.

Hornak, J., Rolls, E.T., Wade, D. 1996. Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. *Neuropsychologia* 34: 247 – 261.

Hornak, J., Bramham, J., Rolls, E.T., Morris, R.G., O'Doherty, J., Bullock, P.R., Polkey, C.E. 2003. Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain* 126: 1691 – 1712.

Hubel, D.H., Wiesel, T.N. 1959. Receptive fields of single neurones in the cat's striate cortex. *The Journal of Physiology (London)* 148: 574 – 591.

Huster, R.J., Wolters, C., Wollbrink, A., Schweiger, E., Wittling, W., Pantev, C., Junqhofer, M. 2009. Effects of anterior cingulate fissurization on cognitive control during stroop interference. *Human Brain Mapping* 30 (4): 1279 - 1289.

Huuhka, K., Kampman, O., Anttila, S., Huuhka, M., Rontu, R., Mattila, K.M., Hurme, M., Lehtimäki, T., Leinonen, E. 2008. RGS4 polymorphism and response to electroconvulsive therapy in major depressive disorder. *Neuroscience Letters* 437 (1): 25 – 28.

I

Iidaka, T., Omori, M., Murata, T., Kosaka, H., Yonekura, Y., Okada, T., Sadato, N. 2001. Neural interaction of the amygdala with the prefrontal and temporal cortices in the processing of facial expressions as revealed by fMRI. *Journal of Cognitive Neuroscience* 13: 1035 – 1047.

Iversen, S.D., Mishkin, M. 1970. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Experimental Brain Research* 11 (4): 376 – 386.

J

Jablensky, A. 2003. The epidemiological horizon. In Hirsch, S.R., Weinberger, D.R., editors. *Schizophrenia*, 2nd edition, Blackwell publishing company, Massachusetts, USA. Chapter 12.

Jindal, R.D., Pillai, A.K., Mahadik, S.P., Eklund, K., Montrose, D.M., Keshavan, M.S. 2010. Decreased BDNF in patients with antipsychotic naïve first episode schizophrenia. *Schizophrenia Research* 119 (1 – 3): 47 – 51.

Job, D.E., Whalley, H.C., McConnell, S., Glabus, M., Johnstone, E.C., Lawrie, S.M. 2002. Structural gray matter differences between first-episode schizophrenics and normal controls using voxel-based morphometry. *Neuroimage* 17 (2): 880 – 889.

Jodo, E., Chiang, C., Aston-Jones, G. 1998. Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus neurons. *Neuroscience* 83 (1): 63 – 79.

Johnstone, E.C. 1991. Defining characteristics of schizophrenia. *British Journal of Psychiatry* 13: 5 - 6.

Johnstone, E.C., Abukmeil, S.S., Byrne, M., Clafferty, R., Grant, E., Hodges, A., Lawrie, S.M., Owens, D.G. 2000. Edinburgh high risk study - findings after four years: demographic, attainment and psychopathological issues. *Schizophrenia Research* 46 (1): 1 - 15.

Johnstone, E.C., Cosway, R., Lawrie, S.M. 2002. Distinguishing characteristics of subjects with good and poor early outcome in the Edinburgh High - Risk Study. *The British Journal of Psychiatry* 181: 26 - 29.

Johnstone, E.C., Ebmeier, K.P., Miller, P., Cunningham Owens, D.G., Lawrie, S.M. 2005. Predicting schizophrenia: findings from the Edinburgh High - Risk Study. *The British Journal of Psychiatry* 186: 18 – 25.

Jones, E.G. 1998. Viewpoint: the core and matrix of thalamic organization. *Neuroscience* 85 (2): 331 - 345.

Jönsson, E., Brené, S., Zhang, X.R., Nimgaonkar, V.L., Tylec, A., Schalling, M., Sedvall, G. 1997. Schizophrenia and neurotropin–3 alleles. *Acta Psychiatrica Scandinavica* 95 (5): 414 – 419.

Jönsson, E.G., Flyckt, L., Burgert, E., Crocq, M.A., Forslund, K., Mattila-Evenden, M., Rylander, G., Asberg, M., Nimgaonkar, V.L., Edman, G., Bjerkenstedt, L., Wiesel, F.A., Sedvall, G.C. 2003 a. Dopamine D3 receptor gene Ser9Gly variant and schizophrenia: association study and meta-analysis. *Psychiatric genetics* 13 (1): 1 – 12.

Jönsson, E.G., Sedvall, G.C., Nöthen, M.M., Cichon, S. 2003 b. Dopamine D4 receptor gene (DRD4) variants and schizophrenia: meta-analyses. *Schizophrenia research* 61 (1): 111 – 119.

Joo, E.J., Lee, K.Y., Jeong, S.H., Chang, J.S., Ahn, Y.M., Koo, Y.J., Kim, Y.S. 2007. Dysbindin gene variants are associated with bipolar I disorder in a Korean population. *Neuroscience Letters* 418 (3): 272 – 275.

Joyce, E.M., Hutton, S.B., Mutsatsa, S.H., Barnes, T.R.E. 2005. Cognitive heterogeneity in first-episode schizophrenia. *The British Journal of Psychiatry* 187: 516 – 522.

Just, M.A., Cherkassky, V.L., Keller, T.A., Kana, R.K., Minshew, N.J. 2007. Functional and anatomical cortical underconnectivity in autism: Evidence from an fMRI study of an executive function task and corpus callosum morphometry. *Cerebral Cortex* 17 (4): 951 – 961.

K

Kamiya, A., Kubo, K., Tomoda, T., Takaki, M., Youn, R., Ozeki, Y., Sawamura, N., Park, U., Kudo, C., Okawa, M., Ross, C.A., Hatten, M.E., Nakajima, K., Sawa, A. 2005. A schizophrenia-associated mutation of DISC1 perturbs cerebral cortex development. *Nature Cell Biology* 7 (12): 1167 – 1178.

Kato, T. 2007. Molecular genetics of bipolar disorder and depression. *Psychiatry and Clinical Neurosciences* 61 (1): 3 - 19.

Kawashima, K., Ikeda, M., Kishi, T., Kitajima, T., Yamanouchi, Y., Kinoshita, Y., Okochi, T., Aleksic, B., Tomita, M., Okada, T., Kunugi, H., Inada, T., Ozaki, N., Iwata, N. 2009. BDNF is not associated with schizophrenia: Data from a Japanese population study and meta-analysis. *Schizophrenia Research* 112 (1 – 3): 72 – 79.

Kay, S.R., Fiszbein, A., Opler, L.A. 1987. The Positive and Negative Symptom Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* 13 (2): 261 - 276.

Keck, P.E.Jr., McElroy, S.L., Havens, J.R., Altshuler, L.L., Nolen, W.A., Frye, M.A., Suppes, T., Denicoff, K.D., Kupka, R., Leverich, G.S., Rush, A.J., Post,

R.M. 2003. Psychosis in bipolar disorder: phenomenology and impact on morbidity and course of illness. *Comprehensive Psychiatry* 44 (4): 263 - 269.

Kempf, L., Hussain, N., Potash, J.B. 2005. Mood disorder with psychotic features, schizoaffective disorder, and schizophrenia with mood features: trouble at the borders. *International Review of Psychiatry* 17 (1): 9 - 19.

Kendler, K.S., Lieberman, J.A., Walsh, D. 1989. The Structured Interview for Schizotypy (SIS): A Preliminary Report. *Schizophrenia Bulletin* 15 (4): 559 - 571.

Kessler, S. 1980. The genetics of schizophrenia: a review. *Schizophrenia Bulletin* 6 (3): 404 – 416.

Kimbrell, T.A., George, M.S., Parekh, P.I., Ketter, T.A., Podell, D.M., Danielson, A.L., Repella, J.D., Benson, B.E., Willis, M.W., Herscovitch, P., Post, R.M. 1999. Regional brain activity during transient self - induced anxiety and anger in healthy adults. *Biological Psychiatry* 46: 454 – 465.

Klein, J.C., Rushworth, M.F.S., Behrens, T.E.J., Mackay, C.E., de Crespigny, A.J., D'Arceuil, H., Johansen-Berg, H. 2010. Topography of connections between human prefrontal cortex and mediodorsal thalamus studied with diffusion tractography. *NeuroImage* 51: 555 – 564.

Kondo, H., Saleem, K.S., Price, J.L. 2003. Differential connections of the temporal pole with the orbital and medial prefrontal networks in macaque monkeys. *Journal of Comparative Neurology* 465 (4): 499 – 523.

Kostović, I., Jovanov-Milosević, N. 2006. The development of cerebral connections during the first 20 - 45 weeks' gestation. *Seminars in Fetal and Neonatal Medicine* 11 (6): 415 - 422.

Krabbendam, L., Arts, B., van Os, J., Aleman, A. 2005. Cognitive functioning in patients with schizophrenia and bipolar disorder: a quantitative review. *Schizophrenia Research* 80 (2-3): 137 - 149.

Kraepelin, E. 1896. *Psychiatrie: Ein Lehrbuch fur Studirende und Aerzte. Funfte, vollstandig umgearbeitete Auflage*. Leipzig.

Krettek, J.E., Price, J.L. 1977. The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat. *Journal of Comparative Neurology* 171 (2): 157 – 192.

Kringelbach, M.L., Rolls, E.T. 2004. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Progress in Neurobiology* 72: 341 – 372.

Kringelbach, M.L. 2005. The human orbitofrontal cortex: linking reward to hedonic experience. *Nature Reviews. Neuroscience* 6: 691 – 702.

Kruger, S., Seminowicz, D., Goldapple, K., Kennedy, S.H., Mayberg, H.S., 2003. State and trait influences on mood regulation in bipolar disorder: blood flow differences with an acute mood challenge. *Biological Psychiatry* 54: 1274 – 1283.

Kubicki, M., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Kasai, K., Kikinis, R., Jolesz, F.A., McCarley, R.W. 2002. Voxel-Based Morphometric Analysis of Grey matter in first episode schizophrenia. *Neuroimage* 17 (4): 1711 – 1719.

Kutcher, S., Robertson, H.A., Bird, D. 1998. Premorbid functioning in adolescent onset bipolar I disorder: a preliminary report from an ongoing study. The Journal of Affective Disorders 51: 137 – 144.

L

Lacerda, A.L.T., Keshavan, M.S., Hardan, A.Y., Yorbik, O., Brambilla, P., Sassi, R.B., Nicoletti, M., Mallinger, A.G., Frank, E., Kupfer, D.J., Soares, J.C. 2004. Anatomic Evaluation of the Orbitofrontal Cortex in Major Depressive Disorder. *Biological Psychiatry* 55: 353 – 358.

Lacerda, A.L., Hardan, A.Y., Yorbik, O., Vemulapalli, M., Prasad, K.M., Keshavan, M.S. 2007. Morphology of the orbitofrontal cortex in first-episode schizophrenia: relationship with negative symptomatology. *Progress in Neuropsychopharmacology and Biological Psychiatry* 31: 510 – 516.

Lai, T., Payne, M.E., Byrum, C.E., Steffens, D.C., Krishnan, K.R. 2000. Reduction of orbital frontal cortex volume in geriatric depression. *Biological Psychiatry* 48: 971 – 975.

Larminie, C., Murdock, P., Walhin, J.P., Duckworth, M., Blumer, K.J., Scheideler, M.A., Garnier, M. 2004. Selective expression of regulators of G-protein signaling (RGS) in the human central nervous system. *Brain Research. Molecular Brain Research.* 122 (1): 24 – 34.

Laruelle, M., Kegeles, L.S., Abi-Dargham, A. 2003. Glutamate, dopamine, and schizophrenia: from pathophysiology to treatment. *Annals of the New York Academy of Sciences* 1003: 138 - 158.

Lawrie, S.M., Abukmeil, S.S. 1998. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. *British Journal of Psychiatry* 172: 110 - 120.

Lawrie, S.M., Whalley, H.C., Abukmeil, S.S., Kestelman, J.N., Donnelly, L., Miller, P., Best, J.J., Owens, D.G., Johnstone, E.C. 2001. Brain structure, genetic liability and psychotic symptoms in subjects at high risk of developing schizophrenia. *Biological Psychiatry* 49 (10): 811 – 823.

Leonard, C.M., Towler, S., Welcome, S., Chiarello, C. 2009. Paracingulate asymmetry in anterior and midcingulate cortex: sex differences and the effect of measurement technique. *Brain Structure and Function* 213: 553 – 569.

Leslie, A.M.1987. Pretense and representation: the origins of 'theory of mind'. *Psychological review* 94 (4): 412 – 426.

Leslie, A. 1991. The theory of mind impairment in autism: Evidence for a modular mechanism of development? In A. Whiten, (ed.), *Natural theories of mind.* Oxford, UK: Basil Blackwell.

Levesque, J., Eugene, F., Joanette, Y., Paquette, V., Mensour, B., Beaudoin, G., Leroux, J.M., Bourgouin, P., Beauregard, M. 2003. Neural circuitry underlying voluntary suppression of sadness. *Biological Psychiatry* 53: 502 – 510.

Lewis, C.M., Levinson, D.F., Wise, L.H., DeLisi, L.E., Straub, R.E., Hovatta, I., Williams, N.M., Schwab, S.G., Pulver, A.E., Faraone, S.V., Brzustowicz, L.M., Kaufmann, C.A., Garver, D.L., Gurling, H.M., Lindholm, E., Coon, H., Moises, H.W., Byerley, W., Shaw, S.H., Mesen, A., Sherrington, R., O'Neill, F.A., Walsh, D., Kendler, K.S., Ekelund, J., Paunio, T., Lönnqvist, J., Peltonen, L., O'Donovan, M.C., Owen, M.J., Wildenauer, D.B., Maier, W., Nestadt, G., Blouin, J.L., Antonarakis, S.E., Mowry, B.J., Silverman, J.M., Crowe, R.R., Cloninger, C.R., Tsuang, M.T., Malaspina, D., Harkavy-Friedman, J.M., Svrakic, D.M., Bassett, A.S., Holcomb, J., Kalsi, G., McQuillin, A., Brynjolfson, J., Sigmundsson, T., Petursson, H., Jazin, E., Zoëga, T., Helgason, T. 2003. Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. *American Journal of Human Genetics* 73 (1): 34 – 48.

Lezak, M.D. 1983. *Neuropsychological assessment* (2nd ed.). New York: Oxford University Press.

Lezak, M.D. 1995. *Neuropsychological Assessment* (3rd ed.). New York: Oxford University Press.

Likhtik, E., Pelletier, J.G., Paz, R., Pare, D. 2005. Prefrontal control of the amygdala. *Journal of Neuroscie*nce 25 (32): 7429 – 7437.

Liotti, M., Mayberg, H.S., McGinnis, S., Brannan, S.L., Jerabek, P. 2002. Unmasking Disease - specific cerebral blood flow abnormalities: Mood

challenge in patients with remitted unipolar depression. *The American Journal of Psychiatry* 159: 1830 – 1840.

Lipschutz, B., Friston, K.J., Ashburner, J., Turner, R., Price, C.J. 2001. Assesing study-specific regional variations in fMRI signal. *Neuroimage* 13: 392 – 398.

Lipska, B.K., Peters, T., Hyde, T.M., Halim, N., Horowitz, C., Mitkus, S., Weickert, C.S., Matsumoto, M., Sawa, A., Straub, R., Vakkalanka, R., Herman, M.M., Weinberger, D.R., Kleinman, J.E. 2006. Expression of DISC1 binding partners is reduced in schizophrenia and associated with DISC1 SNPs. *Human Molecular Genetics.* 15 (8): 1245 - 1258.

Liu, X., He, G., Wang, X., Chen, Q., Qian, X., Lin, W., Li, D., Gu, N., Feng, G., He, L. 2004. Association of DAAO with schizophrenia in the Chinese population. *Neuroscience Letters* 369 (3): 228 – 233.

Lodge, D.J. 2011. The medial prefrontal and orbitofrontal cortices differentially regulate dopamine system function. *Neuropsychopharmacology* 36 (6): 1227 – 1236.

London, E.D., Ernst, M., Grant, S., Bonson, K., Weinstein, A. 2000. Orbitofrontal cortex and human drug abuse: functional imaging. *Cerebral Cortex* 10: 334 – 342.

Long, F., Wu, T., Movellan, J.R., Bartlett, M.S., Littlewort, G. 2012. Learning spatiotemporal features by using independent component analysis with application to facial expression recognition. *Neurocomputing* 93: 126 – 132.

Lopez - Larson, M.P., DelBello, M.P., Zimmerman, M.E., Schwiers, M.L., Strakowski, S.M. 2002. Regional prefrontal gray and white matter abnormalities in bipolar disorder. *Biological Psychiatry* 52: 93 – 100.

Lough, S., Kipps, C.M., Treise, C., Watson, P., Blair, J.R., Hodges, J.R. 2006. Social reasoning, emotion and empathy in frontotemporal dementia. *Neuropsychologia* 44 (6): 950 – 958.

Lucey, J.V. 2001. The neuroanatomy of OCD. In Fineberg, N., Mazzin, D., Stein, D.J. (eds). *Obsessive - compalsive disorder: A practical guide*. Pp. 77 - 87. London: M. Donitz.

M

Ma, J., Sun, J., Zhang, H., Zhang, R., Kang, W.-H., Gao, C.-G., Liu, H.-S., Ma, X.-H., Min, Z.-X., Zhao, W.-X., Ning, Q.-L., Wang, S.-H., Zhang, Y.-C., Guo, T.-W., Lu, S.-M. 2009. Evidence for transmission disequilibrium at the

DAOA gene locus in a schizophrenia family sample. *Neuroscience Letters* 462 (2): 105 – 108.

MacFall, J.R., Payne, M.E., Provenzale, J.E., Krishnan, K.R. 2001. Medial orbital frontal lesions in late-onset depression. *Biological Psychiatry* 49: 803 – 806.

Mackie, S., Millar, J.K., Porteous, D.J. 2007. Role of DISC1 in neural development and schizophrenia. *Current Opinion in Neurobiology* 17: 95 - 102.

Madeira, C., Freitas, M.E., Vargas-Lopes, C., Wolosker, H., Panizzutti, R. 2008. Increased brain d-amino acid oxidase (DAAO) activity in schizophrenia. *Schizophrenia Research* 101 (1 – 3): 76 – 83.

Maeda, K., Nwulia, E., Chang, J., Balkissoon, R., Ishizuka, K., Chen, H., Zandi, P., McInnis, M.G., Sawa, A. 2006. Differential Expression of Disrupted-in-Schizophrenia (DISC1) in Bipolar Disorder. *Biological Psychiatry* 60 (9): 929 – 935.

Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H. 2003. An automated method for neuroanatomic and cytoarchitectonic atlas - based interrogation of fMRI data sets. *Neuroimage* 19: 1233 – 1239.

Mangin, J.-F., Frouin, V., Bloch, I., Régis, J., López-Krahe, J. 1995. 3D magnetic resonance images to structural representations of the cortex topography using topology preserving deformations. *Journal of Mathematical Imaging and Vision* 5 (4): 297 – 318.

Mangin, J.-F., Régis, J., Frouin, V. 1996. Shape bottlenecks and conservative flow systems. In *Proc. IEEE Workshop MMBIA*, San Francisco, CA, pp. 319 – 328.

Mangin, J.-F., Coulon, O., Frouin, V. 1998. Robust brain segmentation using histogram scale-space analysis and mathematical morphology. In *Lecture Notes in Computer Science*, Wells, W.M., Colchester, A., Delp, S., Eds. Boston, MA: Springer-Verlag, vol. 1496, Proc. 1st MICCAI, pp. 1230 – 1241.

Mangin, J.-F. 2000. Entropy minimization for automatic correction of intensity Nonuniformity. in *Proc. IEEE Workshop MMBIA*, Hilton Head Island, S.C., pp. 162 – 169.

Mangin, J.-F., Rivière, D., Cachia, A., Duchesnay, E., Cointepas, Y., Papadopoulos-Orfanos, D., Collins, D.L., Evans, A.C., Régis, J. 2004 a. Object-Based Morphometry of the Cerebral Cortex. *IEEE Transactions on medical imaging* 23 (8): 968 – 982.

Mangin, J.-F., Rivière, D., Cachia, A., Duchesnay, E., Cointepas, Y., Papadopoulos-Orfanos, D., Scifo, P., Ochiai, T., Brunelle, F., Régis, J. 2004 b. A framework to study the cortical folding patterns. *NeuroImage* 23 (1): S129 - S138.

Mansfield, P. 1977. Multiplanar image formation using NMR spin echoes. *The Journal of Physical Chemistry* 10: 55 – 58.

Markowitsch, H.J., Vandekerckhove, M.M., Lanfermann, H., Russ, M.O. 2003. Engagement of lateral and medial prefrontal areas in the ecphory of sad and happy autobiographical memories. Cortex 39 (4-5): 643 – 665.

Mayberg, H.S., Starkstein, S.E., Sadzot, B., Preziosi, T., Andrezejewski, P.L., Dannals, R.F., Wagner, H.N.Jr, Robinson, R.G. 1990. Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. *Annals of Neurology* 28 (1): 57 – 64.

McDonald, C., Marshall, N., Sham, P.C., Bullmore, E.T., Schulze, K., Chapple, B., Bramon, E., Filbey, F., Quraishi, S., Walshe, M., Murray, R.M. 2006. Regional brain morphometry in patients with schizophrenia or bipolar disorder and their unaffected relatives. *The American Journal of Psychiatry* 163 (3): 478 – 487.

McGuffin, P., Farmer, A., Harvey, I. 1991. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. *Archives of General Psychiatry* 48 (8): 764 - 770.

McIntosh, A.M., Job, D.E., Moorhead, T.W., Harrison, L.K., Forrester, K., Lawrie, S.M., Johnstone, E.C. 2004. Voxel - based morphometry of patients with schizophrenia or bipolar disorder and their unaffected relatives. *Biological Psychiatry* 56: 544 – 552.

McIntosh, A.M., Job, D.E., Moorhead, T.W., Harrison, L.K., Lawrie, S.M., Johnstone, E.C. 2005. White matter density in patients with schizophrenia, bipolar disorder and their unaffected relatives. *Biological Psychiatry* 58: 254 – 257.

McIntosh, A.M., Job, D.E., Moorhead, W.J., Harrison, L.K., Whalley, H.C., Johnstone, E.C., Lawrie, S.M. 2006. Genetic liability to schizophrenia or bipolar disorder and its relationship to brain structure. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 141: 76 – 83.

McIntosh, A.M., Whalley, H.C., McKirdy, J., Hall, J., Sussmann, J.E., Shankar, P., Johnstone, E.C., Lawrie, S.M. 2008. Prefrontal function and activation in bipolar disorder and schizophrenia. *The American Journal of Psychiatry* 165 (3): 378 - 384.

McNamara, R.K., Jandacek, R., Rider, T., Tso, P., Stanford, K.E., Hahn, C.G., Richtand, N.M. 2008. Deficits in docosahexaenoic acid and associated elevations in the metabolism of arachidonic acid and saturated fatty acids in the postmortem orbitofrontal cortex of patients with bipolar disorder. *Psychiatry Research* 160 (3): 285 - 299.

Mechelli, A., Prata, D.P., Fu, C.H., Picchioni, M., Kane, F., Kalidindi, S., McDonald, C., Demjaha, A., Kravariti, E., Toulopoulou, T., Murray, R., Collier, D.A., McGuire, P.K. 2008. The effects of neuregulin1 on brain function in controls and patients with schizophrenia and bipolar disorder. *Neuroimage* 42 (2): 817 - 826.

Meredith, S.M., Whyler, N.C.A., Stanfield, A., Chakirova, G., Moorhead, T.W.J., Job, D.E., Giles, S., McIntosh, A.M., Johnstone, E.C., Lawrie, S.M. 2012. Anterior cingulate morphology in people at genetic high-risk of schizophrenia. *European Psychiatry* 27 (5): 377 - 385.

Mesulam, M.-M., Mufson, E.J. 1982. Insula of the old world monkey. III Efferent cortical output and comments on function. *The Journal of Comparative Neurology* 212: 38 – 52.

Mesulam, M.-M., Mufson, E.J. 1984. Neural inputs into the nucleus basalis of the substantia innominata in the rhesus monkey. *Brain* 107: 253 – 274 (Chapter 4).

Miguel-Hidalgo, J.J., Waltzer, R., Whittom, A.A., Austin, M.C., Rajkowska, G., Stockmeier, C.A. 2010. Glial and glutamatergic markers in depression, alcoholism, and their comorbidity. *Journal of Affective Disorders* 127: 230 – 240.

Millar, J.K., Pickard, B.S., Mackie, S., James, R., Christie, S., Buchanan, S.R., Malloy, M.P., Chubb, J.E., Huston, E., Baillie, G.S., Thomson, P.A., Hill, E.V., Brandon, N.J., Rain, J., Camargo, L.M., Whiting, P.J., Houslay, M.D., Blackwood, D.H.R., Muir, W.J., Porteous, D.J. 2005. DISC1 and PDE4B are interacting genetic factors in schizophrenia that regulate cAMP signaling. *Science* 310 (5751): 1187 -1191.

Miller, P., Byrne, M., Hodges, A., Lawrie, S.M., Owens, D.G.C., Johnstone, E.C. 2002. Schizotypal components in people at the high risk of developing schizophrenia: early findings from the Edinburgh High - Risk Study. *The British Journal of Psychiatry* 180: 179 – 184.

Milner, B. 1963. Effect of Different Brain Lesions on Card Sorting. *Archives of Neurology* 9: 90 - 100.

Mitchell, P.B., Meiser, B., Wilde, A., Fullerton, J., Donald, J., Wilhelm, K., Schofield, P.R. 2010. Predictive and diagnostic genetic testing in Psychiatry. *Psychiatric Clinics of North America* 33 (1): 225 – 243.

Moghaddam, B. 2002. Stress activation of glutamate neurotransmission in the prefrontal cortex: implications for dopamine-associated psychiatric disorders. *Biological Psychiatry* 51 (10): 775 – 787.

Moorhead, T.W.J., Job, D.E., Whalley, H.C., Sanderson, T.L., Johnstone, E.C., Lawrie, S.M. 2004. Voxel-based morphometry of comorbid schizophrenia and learning disability: analyses in normalized and native spaces using parametric and nonparametric statistical methods. *NeuroImage* 22 (1): 188 – 202.

Moorhead, T.W., Job, D.E., Spencer, M.D., Whalley, H.C., Johnstone, E.C., Lawrie, S.M. 2005. Empirical comparison of maximal voxel and non-isotropic adjusted cluster extent results in a voxel - based morphometry study of comorbid learning disability with schizophrenia. *Neuroimage* 28: 544 - 552.

Moorhead, T.W., Harris, J.M., Stanfield, A.C., Job, D.E., Best, J.J.K., Johnstone, E.C., Lawrie, S.M. 2006. Automated computation of the gyrification index in prefrontal lobes: methods and comparison with manual implementation. *Neuroimage* 31: 1560 – 1566.

Morecraft, R.J., Geula, C., Mesulam, M.M. 1992. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. *The Journal of Comparative Neurology* 323 (3): 341 – 358.

Morrison, A.P., Frame, L., Larkin, W. 2003. Relationships between trauma and psychosis: A review and integration. *British Journal of Clinical Psychology* 42: 331 – 353.

Mountcastle, V. 1997. The columnar organization of the neocortex. *Brain* 120: 701 - 722.

Murray, C.J., Lopez, A.D. 1996. Evidence based health policy – lessons from the Global Burden of Disease Study. *Science* 274: 740 - 743.

Murray, C.J., Lopez, A.D. 1997. Global mortality, disability, and the contribution of risk factors. Global Burden of Disease Study. *Lancet* 349 (9063): 1436 – 1442.

Murray, R.M., Sham, P., Van Os, J., Zanelli, J., Cannon, M., McDonald, C. 2004. A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophrenia Research* 71 (2 - 3): 405 - 416.

N

Nakamura, K., Sekine, Y., Ouchi, Y., Tsujii, M., Yoshikawa, E., Futatsubashi, M., Tsuchiya, K.J., Sugihara, G., Iwata, Y., Suzuki, K., Matsuzaki, H., Suda, S., Sugiyama, T., Takei, N., Mori, N. 2010. Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. *Archives of General Psychiatry* 67 (1): 59 - 68.

Nakamura, M., Nestor, P.G., McCarley, R.W., Levitt, J.J., Hsu, L., Kawashima, T., Niznikiewicz, M., Shenton, M.E. 2007. Altered orbitofrontal sulcogyral pattern in schizophrenia. *Brain* 130: 693 - 707.

Nakamura, M., Nestor, P.G., Levitt, J.J., Cohen, A.S., Kawashima, T., Shenton, M.E., McCarley, R.W. 2008. Orbitofrontal volume deficit in schizophrenia and thought disorder. *Brain* 131: 180 – 195.

Narr, K.L., Szeszko, P.R., Lencz, T., Woods, R.P., Hamilton, L.S., Phillips, O., Robinson, D., Burdick, K.E., DeRosse, P., Kucherlapati, R., Thompson, P.M., Toga, A.W., Malhotra, A.K., Bilder, R.M. 2009. DTNBP1 is associated with imaging phenotypes in schizophrenia. *Human Brain Mapping* 30 (11): 3783 - 3794.

Nelson, H.E. 1976. Modified card sorting test sensitive to frontal - lobe deficits. *Cortex* 12: 313 – 324.

Nelson, H. 1982. National Adult Reasoning Test. Windsor, Berks: NFER-Nelson.

New, A.S., Buchsbaum, M.S., Hazlett, E.A., Goodman, M., Koenigsberg, H.W., Lo, J., Iskander, L., Newmark, R., Brand, J., O'Flynn, K., Siever, L.J. 2004. Fluoxetine increases relative metabolic rate in prefrontal cortex in impulsive aggression. *Psychopharmacology* (Berl) 176: 451 – 458.

Newberg, A.R., Catapano, L.A., Zarate, C.A., Manji, H.K. 2008. Neurobiology of bipolar disorder. *Expert Review of Neurotherapeutics* 8 (1): 93 – 110.

Nicodemus, K.K., Callicott, J.H., Higier, R.G., Luna, A., Nixon, D.C., Lipska, B.K., Vakkalanka, R., Giegling, I., Rujescu, D., Clair, D.S., Muglia, P., Shugart, Y.Y., Weinberger, D.R. 2010. Evidence of statistical epistasis between DISC1, CIT and NDEL1 impacting risk for schizophrenia: biological validation with functional neuroimaging. *Human Genetics* 127 (4): 441 - 452.

Northoff, G., Richter, A., Gessner, M., Schlagenhauf, F., Fell, J., Baumgart, F., Kaulisch, T., Kötter, R., Stephan, K.E., Leschinger, A., Hagner, T., Bargel, B., Witzel, T., Hinrichs, H., Bogerts, B., Scheich, H., Heinze, H.J. 2000. Functional dissociation between medial and lateral prefrontal cortical

spatiotemporal activation in negative and positive emotions: A combined fMRI/MEG study. *Cerebral Cortex* 10: 93 – 107.

Numakawa, T., Yagasaki, Y., Ishimoto, T., Okada, T., Suzuki, T., Iwata, N., Ozaki, N., Taguchi, T., Tatsumi, M., Kamijima, K., Straub, R.E., Weinberger, D.R., Kunugi, H., Hashimoto, R. 2004. Evidence of novel neuronal functions of dysbindin, a susceptibility gene for schizophrenia. *Human Molecular Genetics* 13 (21): 2699 –2708.

Nyhus, E., Barcelo, F. 2009. The Wisconsin Card Sorting Test and the cognitive assessment of prefrontal executive function: a critical update. *Brain and cognition* 71: 437 – 451.

O

O'Doherty, J., Kringelbach, M.L., Rolls, E.T., Hornak, J., Andrews, C. 2001. Abstract reward and punishment representations in the human orbitofrontal cortex. *Nature Neuroscience* 4 (1): 95 – 102.

Ogawa, S., Lee, T.M., Kay, A.R., Tank, D.W. 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America* 87 (24): 9868 – 9872.

Ojemann, J.C., Akbudak, E., Snyder, A.Z., McKinstry, R.C., Raichle, M.E., Conturo, T.E. 1997. Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artefacts. *Neuroimage* 6: 156 – 167.

Ongur, D., An, X., Price, J.L. 1998. Prefrontal cortical projections to the hypothalamus in macaque monkeys. *The Journal of Comparative Neurology* 401 (4): 480 – 505.

Ongur, D., Price, J.L. 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex* 10: 206 – 219.

Opgen-Rhein, C., Lencz, T., Burdick, K.E., Neuhaus, A.H., DeRosse, P., Goldberg, T.E., Malhotra, A.K. 2008. Genetic variation in the DAOA gene complex: Impact on susceptibility for schizophrenia and on cognitive performance. *Schizophrenia Research* 103 (1 – 3): 169 – 177.

Ossmann, J.M., Mulligan, N.W. 2003. Inhibition and attention deficit hyperactivity disorder in adults. *The American Journal of Psychology* 116 (1): 35 – 50.

Overall, J.E., Gorham, D.R. 1962. The brief psychiatric rating scale. *Psychological Reports* 10: 799 – 812.

Owens, D.G.C., Johnstone, E.C. 2006. Precursors and prodromata of schizophrenia: findings from the Edinburgh High Risk Study and their literature context. *Psychological Medicine* 36 (11): 1501 – 1514.

P

Palo, O.M., Antila, M., Silander, K., Hennah, W., Kilpinen, H., Soronen, P., Tuulio-Henriksson, A., Kieseppä, T., Partonen, T., Lönnqvist, J., Peltonen, L., Paunio, T. 2007. Association of distinct allelic haplotypes of DISC1 with psychotic and bipolar spectrum disorders and with underlying cognitive impairments. *Human Molecular Genetics* 16 (20): 2517 – 2528.

Pang, A., Lewis, S.W. 1996. Bipolar Affective Disorder Minus Left Prefrontal Cortex Equals Schizophrenia. *British Journal of Psychiatry* 168: 647 - 650.

Pantelis, C., Velakoulis, D., McGorry, P.D., Wood, S.J., Suckling, J., Phillips, L.J., Yung, A.R., Bullmore, E.T., Brewer, W., Soulsby, B., Desmond, P., McGuire, P.K. 2003. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 361 (9354): 281 – 288.

Papagni, S.A., Mechelli, A., Prata, D.P., Kambeitz, J., Fu, C.H.Y., Picchioni, M., Walshe, M., Toulopoulou, T., Bramon, E., Murray, R.M., Collier, D.A., Bellomo, A., McGuire, P. 2011. Differential effects of DAAO on regional activation and functional connectivity in schizophrenia, bipolar disorder and controls. *NeuroImage* 56 (4): 2283 – 2291.

Pardo, J.V., Pardo, P.J., Raichle, M.E. 1993. Neural correlates of self-induced dysphoria. *American Journal of Psychiatry* 150: 713 – 719.

Passingham, R.E., Toni, I., Rushworth, M.F. 2000. Specialization within the prefrontal cortex: the ventral prefrontal cortex and associative learning. *Experimental Brain Research* 133 (1): 103 – 113.

Paterlini, M., Zakharenko, S.S., Lai, W.S., Qin, J., Zhang, H., Mukai, J., Westphal, K.G., Olivier, B., Sulzer, D., Pavlidis, P., Siegelbaum, S.A., Karayiorgou, M., Gogos, J.A. 2005. Transcriptional and behavioral interaction between 22q11.2 orthologs modulates schizophrenia-related phenotypes in mice. *Nature Neuroscience* 8 (11): 1586–1594.

Pauling, L., Coryell, C.D. 1936. The magnetic properties and structure of the hemochromogens and related structures. *Proceedings of the National Academy of Sciences* 22: 159 – 163.

Paus, T., Tomaiuolo, F., Otaky, N., MacDonald, D., Petrides, M., Atlas, J., Morris, R., Evans, A.C. 1996. Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. *Cerebral Cortex* 6: 207 – 214.

Pelletier, M., Bouthillier, A., Lévesque, J., Carrier, S., Breault, C., Paquette, V., Mensour, B., Leroux, J.M., Beaudoin, G., Bourgouin, P., Beauregard, M.J., Paquette, V., Mensour, B., Leroux, J.M., Beaudoin, G., Bourgouin, P., Beauregard, M. 2003. Separate neural circuits for primary emotions? Brain activity during self-induced sadness and happiness in professional actors. *NeuroReport* 14: 1111 – 1116.

Perrett, E. 1974. The left frontal lobe of man and the suppression of habitual responses in verbal categorical behavior. *Neuropsychologia* 12: 323 – 330.

Perrot, M., Rivière, D., Mangin, J.-F. 2011. Cortical sulci recognition and spatial normalization. *Medical Image Analysis* 15 (4): 529 - 550.

Petrides, M., Pandya, D.P. 1994. Comparative architectonic analysis of the human and macaque frontal cortex. In: Grafman, J., Boller, F., editors. Handbook of neuropsychology. *Amsterdam: Elsevier.* 17 – 58.

Petrides, M. 1996. Specialized systems for the processing of mnemonic information within the primate frontal cortex. *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences* 351 (1346): 1455 - 1461; discussion 1461 - 1462.

Petrides, M. 2005. Lateral prefrontal cortex: architectonic and functional organization. *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences* 360 (1456): 781 – 795.

Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R. 2003. Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biological Psychiatry* 54 (5): 515 - 528.

Phillips, M.L., Vieta, E. 2007. Identifying functional neuroimaging biomarkers of bipolar disorder: Toward DSM - V. *Schizophrenia Bulletin* 33: 893 – 904.

Phillips, M.L., Ladouceur, C.D., Drevets, W.C. 2008. A neural model of voluntary and automatic emotion regulation: Implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Molecular Psychiatry* 13 (9): 829, 833 - 857.

Pomarol – Clotet, E., Fatjo – Vilas, M., McKenna, P.J., Monte, G.C., Sarro, S., Ortiz – Gil, J., Aguirre, C., Gomar, J.J., Guerrero, A., Landin, R., Capdevila, A., Fañanás, L., Salvador, R. 2010. COMT Val158Met polymorphism in relation to activation and de-activation in the prefrontal

cortex: A study in patients with schizophrenia and healthy subjects. *Neuroimage* 53 (3): 899 - 907.

Prata, D.P., Mechelli, A., Fu, C.H.Y., Picchioni, M., Kane, F., Kalidini, S., McDonald, C., Howes, O., Kravariti, E., Demjaha, A., Toulopoulou, T., Diforti, M., Murray, R.M., Collier, D.A., McGuire, P.K. 2009. Opposite effects of Catechol-O-Methyltransferase Val158Met on cortical function in healthy subjects and patients with schizophrenia. *Biological Psychiatry* 65 (6): 473 – 480.

Prata, D.P., Mechelli, A., Picchioni, M., Fu, C.H., Kane, F., Kalidindi, S., McDonald, C., Kravariti, E., Toulopoulou, T., Bramon, E., Walshe, M., Murray, R., Collier, D.A., McGuire, P.K. 2011. No association of Disrupted-in-Schizophrenia-1 variation with prefrontal function in patients with schizophrenia and bipolar disorder. *Genes, Brain and Behavior* 10 (3): 276 – 285.

Price, J.L. 1985. Beyond the olfactory cortex: olfactory - related areas in the neocortex, thalamus and hypothalamus. *Chemical Senses* 10 (2): 239 – 258.

Price, J.L. 1999. Prefrontal cortical networks related to visceral function and mood. *Annals of the New York Academy of Sciences* 877: 383 – 396.

Price, J.L. 2003. The olfactory system. In: *The Human Nervous System*, 2nd ed., Paxinos, G. (ed.) San Diego: Academic Press.

Purcell, E.M., Torrey, H.C., Pound, R.V. 1946. Resonance absorption by nuclear magnetic moments in a solid. *Physiology Reviews* 69: 37.

R

Rahm, B., Opwis, K., Kaller, C.P., Spreer, J., Schwarzwald, R., Seifritz, E., Halsband, U., Unterrainer, J.M. 2006. Tracking the subprocesses of decision-based action in the human frontal lobes. *NeuroImage* 30 (2): 656 – 667.

Rajkowska, G., Miguel – Hidalgo, J.J., Wei, J., Dilley, G., Pittman, S.D., Meltzer, H.Y., Overholser, J.C., Roth, B.L., Stockmeier, C.A. 1999. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biological Psychiatry* 45 (9): 1085 – 1098.

Rajkowska, G. 2000. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biological Psychiatry* 48: 766 – 777.

Rakic, P. 1988. Specification of cerebral cortical areas. *Science* 41: 170 – 176.

Raleigh, M.J., Steklis, H.D. 1981. Effect of orbitofrontal and temporal neocortical lesions of the affiliative behavior of vervet monkeys (*Cercopithecus aethiops sabaeus*). *Experimental Neurology* 73: 378 – 389.

Rametti, G., Junqué, C., Bartrés-Faz, D., Zubiaurre-Elorza, L., Catalán, R., Penadés, R., Bargalló, N., Bernardo, M. 2010. Anterior cingulate and paracingulate sulci morphology in patients with Schizophrenia. *Schizophrenia Research* 121: 66 – 74.

Ray, J.P., Price, J.L. 1992. The organization of the thalamocortical connections of the mediodorsal thalamic nucleus in the rat, related to the ventral forebrain-prefrontal cortex topography. *The Journal of Comparative Neurology* 323 (2): 167 - 197.

Ray, J.P., Price, J.L. 1993. The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in macaque monkeys. *Journal of Comparative Neurology* 337: 1 – 31.

Raybould, R., Green, E.K., MacGregor, S., Gordon-Smith, K., Heron, J., Hyde, S., Caesar, S., Nikolov, I., Williams, N., Jones, L., O'Donovan, M.C., Owen, M.J., Jones, I., Kirov, G., Craddock, N. 2005. Bipolar disorder and polymorphisms in the dysbindin gene (DTNBP1). *Biological Psychiatry* 57 (7): 696 – 701.

Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., Goodwin, F.K. 1990. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) study. *Journal of the American Medical Association* 264 (19): 2511 – 2518.

Rempel - Clower, N.L., Barbas, H. 1998. Topographic organization of connections between the hypothalamus and prefrontal cortex in the rhesus monkey. *The Journal of Comparative Neurology* 398: 393 – 419.

Rey, A. 1964. *L'examen clinique en psychologie*. Presses Universitaires de France: Paris.

Riccio, C.A., Reynolds, C.R., Lowe, P.A. 2001. *Clinical applications of continuous performance tests: Measuring attention and impulsive responding in children and adults.* New York: John Wiley.

Ring, H.A., Bench, C.J., Trimble, M.R., Brooks, D.J., Frackowiak, R.S., Dolan, R.J. 1994. Depression in Parkinson's disease. A positron emission study. *The British Journal of Psychiatry* 165: 333 – 339.

Ringen, P.A., Lagerberg, T.V., Birkenaes, A.B., Engn, J., Faerden, A., Jónsdottir, H., Nesvåg, R., Friis, S., Opjordsmoen, S., Larsen, F., Melle, I., Andreassen, O.A. 2008. Differences in prevalence and patterns of substance

use in schizophrenia and bipolar disorder. *Psychological Medicine* 38 (9): 1241 – 1249.

Rivière, D., Mangin, J.-F., Papadopoulos-Orfanos, D., Martinez, J.-M., Frouin, V., Régis, J. 2002. Automatic recognition of cortical sulci of the human brain using a congregation of neural networks. *Medical Image Analysis* 6 (2): 77 – 92.

Rizzolatti, G., Camard, R., Fogassi, L., Gentilucci, M., Luppino, G., Matelli, M. 1988. Functional organization of inferior area 6 in the macaque monkey. Area F5 and the control of distal movements. *Experimental Brain Research* 71: 491 – 507.

Roberts, A.C., Robbins, T.W., Everitt, B.J., Muir, J.L. 1992. A specific form of cognitive rigidity following excitotoxic lesions of the basal forebrain in marmosets. *Neuroscience* 47: 251 – 264.

Roberts, A.C., Wallis, J.D. 2000. Inhibitory control and affective processing in the prefrontal cortex: Neuropsychological studies in the common marmoset. *Cerebral Cortex* 10: 252 – 262.

Roberts, A.C. 2011. The Importance of Serotonin for Orbitofrontal Function. *Biological Psychiatry* 69 (12): 1185 – 1191.

Rogers, R.D., Everitt, B.J., Baldacchino, A., Blackshaw, A.J., Swainson, R., Wynne, K., Baker, N.B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J.F., Sahakian, B.J., Robbins, T.W. 1999. Dissociable deficits in the decision - making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan -depleted normal volunteers: evidence for monoaminergic mechanisms. *Neuropsychopharmacology* 20 (4): 322 - 339.

Rolls, E.T., Hornak, J., Wade, D., McGrath, J. 1994. Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *Journal of Neurology, Neurosurgery and Psychiatry* 57: 1518 – 1524.

Rolls, E.T. 1996. The orbitofrontal cortex. *Philosophical Transactions of the Royal Society of London. Series B: Biological Science* 351: 1433 – 1443 [discussion 1443–1444].

Rolls, E.T. 1999 a. The Brain and Emotion. *Oxford University Press, Oxford*.

Rolls, E.T. 1999 b. The functions of the orbitofrontal cortex. *Neurocase* 5: 301 – 312.

Rolls, E.T. 2005. Taste, olfactory, and food texture processing in the brain, and the control of food intake. *Physiology and Behavior* 85 (1): 45 – 56.

Romanski, L. M. 2004. Domain specificity in the primate prefrontal cortex. *Cognitive, Affective, and Behavioral Neuroscience* 4 (4): 421 – 429.

Roppongi, T., Nakamura, M., Asami, T., Hayano, F., Otsuka, T., Uehara, K., Fujiwara, A., Saeki, T., Hayasaka, S., Yoshida, T., Shimizu, R., Inoue, T., Hirayasu, Y. 2010. Posterior orbitofrontal sulcogyral pattern associated with orbitofrontal cortex volume reduction and anxiety trait in panic disorder. *Psychiatry and Clinical Neurosciences* 64 (3): 318 - 326.

Rosell, D.R., Thompson, J.L., Slifstein, M., Xu, X., Frankle, W.G., New, A.S., Goodman, M., Weinstein, S.R., Laruelle, M., Abi-Dargham, A., Siever, L.J. 2010. Increased Serotonin 2A Receptor Availability in the Orbitofrontal Cortex of Physically Aggressive Personality Disordered Patients. *Biological Psychiatry* 67: 1154 – 1162.

Ross, E.M., Wilkie, T.M. 2000. GTPase-activating proteins for heterotrimeric G proteins: regulators of G protein signaling (RGS) and RGS-like proteins. *Annual Review of Biochemistry* 69: 795 – 827.

Rubio-Garrido, P., Pérez-de-Manzo, F., Porrero, C., Galazo, M.J., Clascá, F. 2009. Thalamic input to distal apical dendrites in neocortical layer 1 is massive and highly convergent. *Cerebral Cortex* 19 (10): 2380 - 2395.

Ruffman, T., Henry, J.D., Livingstone, V., Phillips, L.H. 2008. A meta-analytic review of emotion recognition and aging: Implications for neuropsychological models of aging. *Neuroscience and Biobehavioral Reviews* 32: 863 – 881.

Russchen, F.T., Amaral, D.G., Price, J.L. 1987. The afferent input to the magnocellular division of the mediodorsal thalamic nucleus in the monkey, Macaca fascicularis. *Journal of Comparative Neurology* 256 (2): 175 – 210.

S

Salmond, C.H., de Haan, M., Friston, K.J., Gadian, D.G., Vargha - Khadem, F. 2003. Investigating individual differences in brain abnormalities in autism. *Philosophical Transactions of the Royal Society of London. Series B: Biological Science* 358: 405 – 413.

Saxena, S., Brody, A.L., Maidment, K.M., Dunkin, J.J., Colgan, M., Alborzian, S., Phelps, M.E., Baxter, L.R. Jr. 1999. Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive-compulsive disorder. *Neuropsychopharmacology* 21: 683 – 693.

Saxena, S., Rauch, S.L. 2000. Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. *The Psychiatric Clinics of North America* 23 (3): 563 - 586.

Schneider, K. 1959. Klinische Psychopathologie. New York/Stuttgart: Thieme Verlag.

Schneider, F., Gur, R.C., Gur, R.E., Shtasel, D.L. 1995. Emotional processing in schizophrenia: neurobehavioral probes in relation to psychopathology. *Schizophrenia Research* 17: 67 – 75.

Schochet, P. 2008. Statistical power for random assignment evaluations of education programs. *Journal of Educational and Behavioral Statistics* 33 (1): 62 - 87.

Schosser, A., Gaysina, D., Cohen – Woods, S., Chow, P.C., Martucci, L., Craddock, N., Farmer, A., Korszun, A., Gunasinghe, C., Gray, J., Schosser, A., Gaysina, D., Cohen - Woods, S., Chow, P.C., Martucci, L., Craddock, N., Farmer, A., Korszun, A., Gunasinghe, C., Gray, J., Jones, L., Tozzi, F., Perry, J., Muglia, P., Owen, M.J., Craig, I.W., McGuffin, P. 2010. Association of DISC1 and TSNAX genes and affective disorders in the depression case-control (DeCC) and bipolar affective case - control (BACCS) studies. *Molecular Psychiatry* 15 (8): 844 - 849.

Schultz, W., Tremblay, L., Hollerman, J.R. 2000. Reward processing in primate orbitofrontal cortex and basal ganglia. *Cerebral Cortex* 10: 272 – 284.

Seltzer, B., Pandya, D.N. 1978. Afferent cortical connections and architectonics of the superior temporal sulcus and surrounding cortex in the rhesus monkey. *Brain Research* 149 (1): 1 – 24.

Shaikh, S., Collier, D.A., Sham, P.C., Ball, D., Aitchison, K., Vallada, H., Smith, I., Gill, M., Kerwin, R.W. 1996. Allelic association between a Ser-9-Gly polymorphism in the dopamine D3 receptor gene and schizophrenia. *Human genetics* 97 (6): 714 – 719.

Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W. 2001. A review of MRI findings in schizophrenia. *Schizophrenia Research* 49 (1 - 2): 1 - 52.

Shi, J., Badner, J.A., Gershon, E.S., Liu, C. 2008. Allelic association of G72/G30 with schizophrenia and bipolar disorder: A comprehensive meta-analysis. *Schizophrenia Research* 98 (1 – 3): 89 – 97.

Shifman, S., Bronstein, M., Sternfeld, M., Pisanté-Shalom, A., Lev-Lehman, E., Weizman, A., Reznik, I., Spivak, B., Grisaru, N., Karp, L., Schiffer, R., Kotler, M., Strous, R.D., Swartz-Vanetik, M., Knobler, H.Y., Shinar, E.,

Beckmann, J.S., Yakir, B., Risch, N., Zak, N.B., Darvasi, A. 2002. A highly significant association between a COMT haplotype and schizophrenia. *American Journal of Human Genetics* 71 (6): 1296 – 1302.

Shimamura, A.P. 2000. The role of prefrontal cortex in dynamic filtering. *Psychobiology* 28 (2): 207 – 218.

Shipp, S. 2007. Structure and function of the cerebral cortex. *Current Biology* 17 (12): 443 – 449.

Silk, T.J., Rinehart, N., Bradshaw, J.L., Tonge, B., Egan, G., O'Boyle, M.W., Cunnington, R. 2006. Visuospatial processing and the function of prefrontal-parietal networks in autism spectrum disorder: A functional MRI study. *American Journal of Psychiatry* 163: 1440 – 1443.

Siris, S.G. 2000. Depression in schizophrenia: perspective in the era of "Atypical" antipsychotic agents*. American Journal of Psychiatry* 157 (9): 1379 - 1389.

Slagle, T.A., Oliphant, M., Gross, S.J. 1989. Cingulate sulcus development in preterm infants. *Pediatric Research* 26: 598 - 602.

Slavchesky, A., Villalpando, J.M., Sarazin, M., Hahn - Barma, V., Pillon, B., Dubois, B. 2004. Frontal assessment battery and differential diagnosis of frontotemporal dementia and Alzheimer disease. *Archives of Neurology* 61 (7): 1104 – 1107.

Slopsema, J.S., Van Der Gugten, J., De Bruin, J.P.C. 1982. Regional concentrations of noradrenaline and dopamine in the frontal cortex of the rat: dopaminergic innervation of the prefrontal subareas and lateralization of prefrontal dopamine. *Brain Research* 250 (1): 197 – 200.

Soeiro-de-Souza, M.G., Bio, D.S., David, D.P., dos Santos Jr., D.R., Kerr, D.S., Gattaz, W.F., Machado-Vieira, R., Moreno, R.A. 2012 a. COMT Met (158) modulates facial emotion recognition in bipolar I disorder mood episodes. *Journal of Affective Disorders* 136 (3): 370 – 376.

Soeiro-de-Souza, M.G., Post, R.M., de Sousa, M.L., Missio, G., do Prado, C.M., Gattaz, W.F., Moreno, R.A., Machado-Vieira, R. 2012 b. Does BDNF genotype influence creative output in bipolar I manic patients? *Journal of Affective Disorders* 139 (2): 181 – 186.

Song, W., Li, W., Noltner, K., Yan, J., Green, E., Grozeva, D., Jones, I.R., Craddock, N., Longmate, J., Feng, J., Sommer, S.S. 2010. Identification of high risk DISC1 protein structural variants in patients with bipolar spectrum disorder. *Neuroscience Letters* 486 (3): 136 – 140.

Spalletta, G., Morris, D.W., Angelucci, F., Rubino, I.A., Spoletini, I., Bria, P., Martinotti, G., Siracusano, A., Bonaviri, G., Bernardini, S., Caltagirone, C., Bossù, P., Donohoe, G., Gill, M., Corvin, A.P. 2010. BDNF Val66Met polymorphism is associated with aggressive behavior in schizophrenia. *European Psychiatry* 25 (6): 311 – 313.

Spreen, O., Strauss, E. 1991. *A Compendium of Neuropsychological Tests*. Oxford University Press: New York.

Stefansson, H., Sigurdsson, E., Steinthorsdottir, V., Bjornsdottir, S., Sigmundsson, T., Ghosh, S., Brynjolfsson, J., Gunnarsdottir, S., Ivarsson, O., Chou, T.T., Hjaltason, O., Birgisdottir, B., Jonsson, H., Gudnadottir, V.G., Gudmundsdottir, E., Bjornsson, A., Ingvarsson, B., Ingason, A., Sigfusson, S., Hardardottir, H., Harvey, R.P., Lai, D., Zhou, M., Brunner, D., Mutel, V., Gonzalo, A., Lemke, G., Sainz, J., Johannesson, G., Andresson, T., Gudbjartsson, D., Manolescu, A., Frigge, M.L., Gurney, M.E., Kong, A., Gulcher, J.R., Petursson, H., Stefansson, K. 2002. Neuregulin 1 and susceptibility to schizophrenia. *American Journal of Human Genetics* 71 (4): 877 – 892.

Stip, E. 1996. Memory impairment in schizophrenia: Perspectives from psychopathology and pharmacotherapy. *Canadian Journal of Psychiatry* 41 (8): 27 – 34.

Stone, V.E., Baron - Cohen, S., Knight, R.T. 1998. Frontal lobe contributions to theory of mind. *Journal of Cognitive Neuroscience* 10: 640 – 656.

Strakowski, S.M., Delbello, M.P., Adler, C.M. 2005. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Molecular Psychiatry* 10 (1): 105 - 116.

Straub, R.E., Jiang, Y., MacLean, C.J., Ma, Y., Webb, B.T., Myakishev, M.V., Harris-Kerr, C., Wormley, B., Sadek, H., Kadambi, B., Cesare, A.J., Gibberman, A., Wang, X., O'Neill, F.A., Walsh, D., Kendler, K.S. 2002. Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. *American Journal of Human Genetics* 71 (2): 337–348.

Strauss, J.S., Carpenter, W.T., Bartko, J.J. 1974. The diagnosis and understanding of schizophrenia: III. Speculations on the processes that underlie schizophrenic symptoms and signs. *Schizophrenia Bulletin* 11: 61 - 75.

Stroop, J.R. 1935. Studies of interference in serial verbal reaction. *Journal of Exprerimental Psychology* 18: 643 - 662.

Stuss, D.T., Gallup Jr., G.G., Alexander, M.P. 2001 a. The frontal lobes are necessary for `theory of mind'. *Brain* 124 (2): 279 - 286.

Stuss, D.T., Floden, D., Alexander, M.P., Levine, B., Katz, D. 2001 b. Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location. Neuropsychologia 39: 771 – 786.

Szeszko, P.R., Hodgkinson, C.A., Robinson, D.G., DeRosse, P., Bilder, R.M., Lencz, T., Burdick, K.E., Napolitano, B., Betensky, J.D., Kane, J.M., Goldman, D., Malhotra, A.K. 2008. DISC1 is associated with prefrontal cortical gray matter and positive symptoms in schizophrenia. *Biological Psychology* 79 (1): 103 – 110.

T

Tabarés-Seisdedos, R., Balanzá-Martínez, V., Sánchez-Moreno, J., Martinez-Aran, A., Salazar-Fraile, J., Selva-Vera, G., Rubio, C., Mata, I., Gómez-Beneyto, M., Vieta, E. 2008. Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. *Journal of Affective Disorders* 109 (3): 286–299.

Takahashi, T., Suzuki, M., Tsunoda, M., Maeno, N., Kawasaki, Y., Zhou, S.Y., Hagino, H., Niu, L., Tsuneki, H., Kobayashi, S., Sasaoka, T., Seto, H., Kurachi, M., Ozaki, N. 2009. The Disrupted-in-Schizophrenia-1 Ser704Cys polymorphism and brain morphology in schizophrenia. *Psychiatry Research* 172 (2): 128 - 135.

Takayanagi, Y., Takahashi, T., Orikabe, L., Masuda, N., Mozue, Y., Nakamura, K., Kawasaki, Y., Itokawa, M., Sato, Y., Yamasue, H., Kasai, K., Okazaki, Y., Suzuki, M. 2010. Volume reduction and altered sulco-gyral pattern of the orbitofrontal cortex in first-episode schizophrenia. *Schizophrenia Research* 121 (1–3): 55 – 65.

Talairach, J., Tournoux, P. 1988. Co-Planar Stereotactic Atlas of the Human Brain. Thieme, Stuttgart/New York.

Talbot, K., Cho, D.S., Ong, W.Y., Benson, M.A., Han, L.Y., Kazi, H.A., Kamins, J., Hahn, C.G., Blake, D.J., Arnold, S.E. 2006. Dysbindin-1 is a synaptic and microtubular protein that binds brain snapin. *Human Molecular Genetics* 15 (20): 3041 - 3054.

Tanabe, T., Iino, M., Takagi, S.F. 1975 a. Discrimination of odors in olfactory bulb, piriform-amigdaloid areas, and orbitofrontal cortex of the monkey. *Journal of Neurophysiology* 38 (5): 1284 – 1296.

Tanabe, T., Yarita, H., Iino, M., Ooshima, Y., Takagi, S.F. 1975 b. An olfactory projection area in orbitofrontal cortex of the monkey. *Journal of Neurophysiology* 38 (5): 1269 – 1283.

Tanaka, D., Nakaya, Y., Yanagawa, Y., Obata, K., Murakami, F. 2003. Multimodal tangential migration of neocortical GABAergic neurons independent of GPI-anchored proteins. *Development* 130 (23): 5803 – 5813.

Tang, J., Xiao, L., Shua, C., Wang, G., Liu, Za., Wang, X., Wang, H., Bai, X. 2008. Association of the brainderived neurotrophic factor gene and bipolar disorder with early age of onset in mainland China. *Neuroscience Letters* 433 (2): 98 – 102.

Taylor, E.M. 1959. The appraisal of children with cerebral deficits. Cambridge, Mass.: Harvard University Press.

Tetko, I.V., Villa, A.E.P. 2001. A pattern grouping algorithm for analysis of spatiotemporal patterns in neuronal spike trains. 2. Application to simultaneous single unit recordings. *Journal of Neuroscience Methods* 105: 15 – 24.

Thomson, P.A., Harris, S.E., Starr, J.M., Whalley, L.J., Porteous, D.J., Deary, I.J. 2005. Association between genotype at an exonic SNP in DISC1 and normal cognitive aging. *Neuroscience Letters* 389 (1): 41 - 45.

Tomppo, L., Hennah, W., Lahermo, P., Loukola, A., Tuulio – Henriksson, A., Suvisaari, J., Partonen, T., Ekelund, J., Lonnqvist, J., Peltonen, L. 2009 a. Association between genes of Disrupted in schizophrenia 1 (DISC1) interactors and schizophrenia supports the role of the DISC1 pathway in the etiology of major mental illnesses. *Biological Psychiatry* 65 (12): 1055 - 1062.

Tomppo, L., Hennah, W., Miettunen, J., Järvelin, M., Veijola, J., Ripatti, S., Lahermo, P., Lichtermann, D., Peltonen, L., Ekelund, J. 2009 b. Association of Variants in DISC1 with Psychosis-Related Traits in a Large Population Cohort. *Archives of General Psychiatry* 66(2): 134 - 141.

Torrey, E.F., Barci, B.M., Webster, M.J., Bartko, J.J., Meador - Woodruff, J.H., Knable, M.B. 2005. Neurochemical markers for schizophrenia, bipolar disorder, and major depression in post-mortem brains. *Biological Psychiatry* 57: 252 – 260.

Tranel, D., Bechara, A., Denburg, N.L. 2002. Asymmetric functional roles of right and left ventromedial prefrontal cortices in social conduct, decision-making, and emotional processing. *Cortex* 38 (4): 589 – 612.

Tsai, G., Coyle, J.T. 2002. Glutamatergic mechanisms in schizophrenia. *Annual Review of Pharmacology and Toxicology* 42: 165 – 179.

Tsuang, M.T., Gilbertson, M.W., Faraone, S.V. 1991. The genetics of schizophrenia. Current knowledge and future directions. *Schizophrenia research* 4 (2): 157 – 171.

Tzourio – Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Tzourio – Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M. 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15: 273 – 289.

U

Uehara – Aoyama, K., Nakamura, M., Asami, T., Yoshida, T., Hayano, F., Roppongi, T., Fujiwara, A., Inoue, T., Shenton, M.E., Hirayasu, Y. 2011. Sexually dimorphic distribution of orbitofrontal sulcogyral pattern in schizophrenia. *Psychiatry and Clinical Neurosciences* 65 (5): 483 - 489.

Uranova, N., Orlovskaya, D., Vikhreva, O., Zimina, I., Kolomeets, N., Vostrikov, V., Rachmanova, V. 2001. Electron microscopy of oligodendroglia in severe mental illness. *Brain Research Bulletin* 55: 597 – 610.

V

Van Hoesen, G.W., Morecraft, R.J., Vogt, B.A. 1993. Connections of the monkey cingulate cortex. In: Vogt, B.A., Gabriel, M. (Eds.), The Neurobiology of the Cingulate Cortex and Limbic Thalamus: A Comprehensive Handbook. *Birkhäuser, Boston.* 249 – 284.

Varrone, A., Pellecchia, M.T., Amboni, M., Sansone, V., Salvatore, E., Ghezzi, D., Garavaglia, B., Brice, A., Brunetti, A., Bonavita, V., De Michele, G., Salvatore, M., Pappata, S., Barone, P. 2004. Imaging of dopaminergic dysfunction with [123I]FP-CIT SPECT in early - onset parkin disease. *Neurology* 63 (11): 2097 – 2103.

Virit, O., Erdal, M.E., Savas, H.A., Barlas, I.O., Yumru, M., Gokdogan, T., Ozen, M.E., Herken, H. 2011. Catechol-O-methyltransferase gene Val108/158Met polymorphism in bipolar disorder. *Neurology, Psychiatry and Brain Research* 17 (2): 46 – 50.

Vogt, B.A., Nimchinsky, E.A., Vogt, L.J., Hof, P.R. 1995. Human cingulate cortex: surface features, flat maps, and cytoarchitecture. *The Journal of Comparative Neurology* 359: 490 - 506.

Vogt, B.A. 2005. Pain and emotion interactions in subregions of the cingulate gyrus. *Nature Reviews Neuroscience* 6 (7): 533 – 544.

Vollm, B.A., Völlm, B.A., Taylor, A.N., Richardson, P., Corcoran, R., Stirling, J., McKie, S., Deakin, J.F., Elliott, R. 2006. Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task. *Neuroimage* 29 (1): 90 – 98.

W

Walker, A.E. 1940. A cytoarchitectural study of the prefrontal area of the macaque monkey. *Journal of Comparative Neurology* 73: 59 – 86.

Walton, M.E., Devlin, J.T., Rushworth, M.F., 2004. Interactions between decision making and performance monitoring within prefrontal cortex. *Nature Neuroscience* 7: 1259 – 1265.

Watanabe, H., Nakamura, M., Ohno, T., Itahashi, T., Tanaka, E., Ohta, H., Yamada, T., Kanai, C., Iwanami, A., Kato, N., Hashimoto, R. 2013. Altered orbitofrontal sulcogyral patterns in adult males with high-functioning autism spectrum disorders. *Social Cognitive and Affective Neuroscience* [Epub ahead of print].

Watson, K.K., Jones, T.K., Allman, J.M. 2006. Dendritic architecture of the von Economo neurons. *Neuroscience* 141: 1107 – 1112.

Way, B.M., Lacan, G., Fairbanks, L.A., Melega, W.P. 2007. Architectonic distribution of the serotonin transporter within the orbitofrontal cortex of the vervet monkey. *Neuroscience* 148: 937 – 948.

Webster, M.J., Bachevalier, J., Ungerleider, L.G. 1994. Connections of inferior temporal areas TEO and TE with parietal and frontal cortex in macaque monkeys. *Cerebral Cortex* 4 (5): 470 – 483.

Whalley, H.C., Kestelman, J.N., Rimmington, J.E., Kelso, A., Abukmeil, S.S., Best, J.J., Johnstone, E.C., Lawrie, S.M. 1999. Methodological issues in volumetric magnetic resonance imaging of the brain in the Edinburgh High Risk Project. *Psychiatry Research: Neuroimaging* 91 (1): 31 – 44.

Whalley, H.C., Simonotto, E., Flett, S., Marshall, I., Ebmeier, K.P., Owens, D.G.C., Goddard, N.H., Johnstone, E.C., Lawrie, S.M. 2004. fMRI correlates of state and trait effects in subjects at genetically enhanced risk of schizophrenia. *Brain* 127: 478 – 490.

Whalley, H.C., Simonotto, E., Marshall, I., Owens, D.G.C., Goddard, N.H., Johnstone, E.C., Lawrie, S.M. 2005 b. Functional disconnectivity in subjects at high genetic risk of schizophrenia. *Brain* 128: 2097 – 2108.

Whitaker-Azmitia, P.M. 2005. Behavioral and cellular consequences of increasing serotonergic activity during brain development: a role in autism? *International Journal of Developmental Neuroscience* 23: 75 - 83.

Whyte, M.-C., Brett, C., Harrison, L.K., Byrne, M., Miller, P., Lawrie, S.M., Johnstone, E.C. 2006. Neuropsychological performance over time in people at high risk of developing schizophrenia and controls. *Biological Psychiatry* 59: 730 – 739.

Williams, P.L., Warwick, R., Dyson, M., Bannister, L.H. 1989. Gray's anatomy. *Edinburgh: Churchill Livingstone.*

Williams, N.M., Preece, A., Morris, D.W., Spurlock, G., Bray, N.J., Stephens, M., Norton, N., Williams, H., Clement, M., Dwyer, S., Curran, C., Wilkinson, J., Moskvina, V., Waddington, J.L., Gill, M., Corvin, A.P., Zammit, S., Kirov, G., Owen, M.J., O'Donovan, M.C. 2004. Identification in 2 independent samples of a novel schizophrenia risk haplotype of the dystrobrevin binding protein gene (DTNBP1). *Archives of General Psychiatry* 61 (4): 336 – 344.

Williams, G.B., Nestor, P.J., Hodges, J.R. 2005. Neural correlates of semantic and behavioural deficits in frontotemporal dementia. *NeuroImage* 24: 1042 - 1051.

Willis, M.L., Palermo, R., Burke, D., McGrillen, K., Miller, L. 2010. Orbitofrontal cortex lesions result in abnormal social judgements to emotional faces. *Neuropsychologia* 48: 2182 – 2187.

Wilson, B.A., Cockburn, J., Baddeley, A.D., Hiorns, R. 1989. The development and validation of a test battery for detecting and monitoring everyday memory problems. *Journal of Clinical and Experimental Neuropsychology* 11: 855 – 870.

Wilson, F.A.W., Scalaidhe, S.P.O., Goldman-Rakic, P.S. 1993. Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science* 260: 1955 – 1958.

Wing, J.K., Cooper, J.E., Sartorius, N. 1974. The description and classification of psychiatric symptoms. An instruction manual for the PSE and CATEGO systems. Cambridge: Cambridge University Press.

Womer, F.Y., Kalmar, J.H., Wang, F., Blumberg, H.P. 2009. Aventral prefrontal - amygdala neural system in bipolar disorder: A view from neuroimaging research. *Acta Neuropsychiatrica* 21: 228 – 238.

World Health Organization. 1992. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: WHO.

World Health Organization. 2001. World health report 2001. Geneva: World Health Organization.

Wright, I.C., Ellison, Z.R., Sharma, T., Friston, K.J., Murray, R.M., McGuire, P.K. 1999. Mapping of grey matter changes in schizophrenia. *Schizophrenia research* 35 (1): 1 – 14.

Y

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A. 1978. A rating scale for mania: reliability, validity and sensitivity. *The British Journal of Psychiatry* 133: 429 – 435.

Young, E.A., Kotun, J., Haskett, R.F., Grunhaus, L., Greden, J.F., Watson, S.J., Akil, H. 1993. Dissociation between pituitary and adrenal suppression to dexamethasone in depression. *Archives of General Psychiatry* 50 (5): 395 – 403.

Young, L.T., Warsh, J.J., Kish, S.J., Shannak, K., Hornykeiwicz, O. 1994. Reduced brain 5-HT and elevated NE turnover and metabolites in bipolar affective disorder. *Biological Psychiatry* 35 (2): 121 – 127.

Young, A.H., Rigney, U., Shaw, S., Emmas, C., Thompson, J.M. 2011. Annual cost of managing bipolar disorder to the UK healthcare system. *Journal of Affective Disorders* 133: 450 – 456.

Yucel, M., Stuart, G.W., Maruff, P., Velakoulis, D., Crowe, S.F., Savage, G., Pantelis, C. 2001. Hemispheric and gender-related differences in the gross morphology of the anterior cingulate/paracingulate cortex in normal volunteers: an MRI morphometric study. *Cerebral Cortex* 11 (1): 17 - 25.

Yucel, M., Wood, S.J., Phillips, L.J., Stuart, G.W., Smith, D.J., Yung, A., Velakoulis, D., McGorry, P.D., Pantelis, C. 2003. Morphology of the anterior cingulate cortex in young men at ultra-high risk of developing a psychotic illness. *The British Journal of Psychiatry* 182: 518 - 524.

Z

Zald, D.H., Kim, S.W. 2001. The orbitofrontal cortex. In: Salloway, S.P., Malloy, P.F., Duffy, J.D., editors. *The Frontal Lobes and Neuropsychiatric Illness.* Washington, DC: American Psychiatric Publishing, 33 – 69.

Zhang, J.-P., Lencz, T., Geisler, S., DeRosse, P., Bromet, E.J., Malhotra, A.K. 2013. Genetic variation in BDNF is associated with antipsychotic

treatment resistance in patients with schizophrenia. *Schizophrenia Research* In Press, Corrected Proof.